

**An empirical study of standards of prevention in South
African HIV vaccine trials:
Norms, perspectives and practices**

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the School of Applied Human Sciences, Discipline of Psychology, College of Humanities,
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DECLARATION

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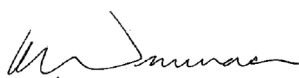
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ABSTRACT

Researchers and sponsors are required to help HIV vaccine trial participants remain HIV-uninfected by ensuring access to HIV risk-reduction interventions, termed the standard of prevention. Ethics guidelines for biomedical HIV prevention trials make a range of recommendations on the standard of prevention, including that participants should be provided with 'state-of-the-art' prevention interventions; what should be declared in protocols and informed consent documents; and about how decisions should be made. Recommendations in these guidelines have been intensely debated, and argued to be infeasible and impractical.

This qualitative study aimed to identify standard of prevention decision-making and implementation practices at five South African trial sites, explore whether practices meet guideline recommendations, and discuss implications for practices and ethics guidelines. Stakeholders' perspectives on key recommendations in ethics guidelines were also explored. Practices were examined through a review of site documents and interviews with key research stakeholders.

Despite concerns in the literature that guidelines establish ideals that cannot be achieved in practice, this study found high concordance between practices and guideline recommendations. In some instances, site practices exceeded recommendations in guidelines. Practices deviated most from guidelines with regard to 'negotiating' standards of prevention packages, the description of prevention plans in protocols and informed consent forms, and the ethical review of monitoring plans.

The 'state-of-the-art' recommendation was argued as being 'in the eye of the beholder' and considered too vague, too absolute and as requiring localisation. The requirement for stakeholder consultation on the evolving standard of prevention was also questioned in terms of who would constitute relevant stakeholders, the difficulties with achieving consensus, and the nature of the consultation process. Stakeholders endorsed ethics requirements that new tools be added to the prevention package when they are scientifically validated and approved by regulatory authorities. In addition, they argued that public health sector availability of the intervention and the phase of the trial also be considered.

Funding restrictions, power inequalities, provider promotion of interventions and cultural dynamics, among other complexities were identified as influencing standards of prevention decision-making and/or implementation. Recommendations are made for strengthened practices and improvements to guidelines so that they address empirically identified complexities.

ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Treatment
AVAC	AIDS Vaccine Advocacy Coalition
CAB	Community Advisory Board
CAG	Community Advisory Group
CDC	United States Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
DoH	Department of Health (South Africa)
DSMB	Data Safety and Monitoring Board
FDA	Food and Drug Administration (USA)
GCM	Global Campaign for Microbicides
GPP	Good Participatory Practice
HIV	Human Immunodeficiency Virus
HCT	HIV Counselling and Testing
HPTN	HIV Prevention Trials Network
HVT	HIV Vaccine Trial

HVTN	HIV Vaccine Trials Network
IAVI	International AIDS Vaccine Initiative
ICAD	Interagency Coalition on AIDS and Development
ICF	Informed Consent Form
P5	Pox-Protein Public-Private Partnership
PI	Principal Investigator
PEP	Post-exposure Prophylaxis
PMTCT	Prevention of mother-to-child-transmission
PrEP	Pre-exposure Prophylaxis
IRB	Institutional Review Board
MCC	Medicines Control Council (South Africa)
MRC	Medical Research Council (South Africa)
NHA	National Health Act (South Africa)
NIH	National Institutes of Health (USA)
NSP	South African National Strategic Plan
REC	Research Ethics Committee (same as IRB).
RTWG	HIV Vaccines and Microbicides Resource Tracking Working Group

SABS	South African Bureau of Standards
SOP	Standard Operating Procedure
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
VCT	Voluntary Counselling and Testing
VMMC	Voluntary Medical Male Circumcision
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
WHO	World Health Organisation

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CHAPTER 1

INTRODUCTION

1. HIV and AIDS: A global snapshot

It is estimated that there are 35.3 million people living with HIV in the world (UNAIDS, 2013), and the global prevalence of HIV among adults is 0.8% (WHO, 2013). The number of new infections in 2012 was 2.3 million worldwide, a significant decrease from the 3.4 million recorded in 2001 (UNAIDS, 2013). Given increasing access to antiretroviral treatment (ART), the number of AIDS deaths have declined to 1.6 million from 2.3 million in 2005 (UNAIDS, 2013). Figure 1 provides a global view of adult HIV prevalence in 2012. Over 95% of all people living with HIV reside in low- and middle-income countries, and Africa remains the continent most affected by HIV.

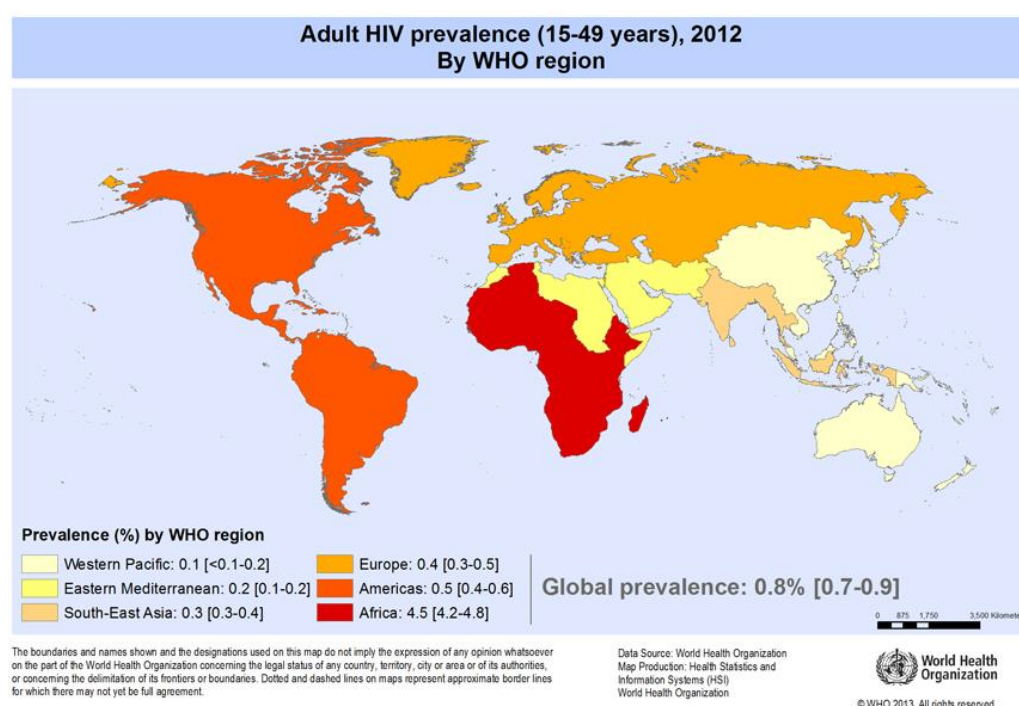


Figure 1: Global adult HIV prevalence by WHO region (WHO, 2013)

2. HIV and AIDS in sub-Saharan Africa

Sub-Saharan Africa bears a disproportionate burden of the HIV/AIDS epidemic. In 2012, 25 million people in sub-Saharan Africa were living with HIV, also home to 70% (1.6 million) of all new HIV infections (UNAIDS, 2013). In 2011, 92% of all pregnant women living with HIV resided in sub-Saharan Africa, as did the more than 90% of children who acquired HIV

in the same year (UNAIDS, 2012). Many countries in the region have shown commendable decreases in HIV infections among young people. However, young girls remain at increased risk for HIV infection (UNAIDS, 2013) with women comprising 58% of those living with HIV in 2011 (UNAIDS, 2012).

In South Africa, an estimated 6.4 million people were living with HIV in 2012 (Shisana et al., 2014) and 240,000 succumbed because of AIDS-related causes (UNAIDS, 2013). With an adult HIV prevalence of 17.9% and 469,000 new infections in 2012 (Shisana et al., 2014), South Africa bears the most severe burden of HIV in the world. Given high prevalence and incidence rates, the epidemic has been characterised as ‘mature, generalized and hyper-endemic’ (Delva & Abdool Karim, 2014, p. 100). The prevalence however, differs according to province (see Figure 2), with KwaZulu-Natal having the highest HIV prevalence in the country at 16.9% compared to 12.2% in the general population (Shisana et al., 2014).

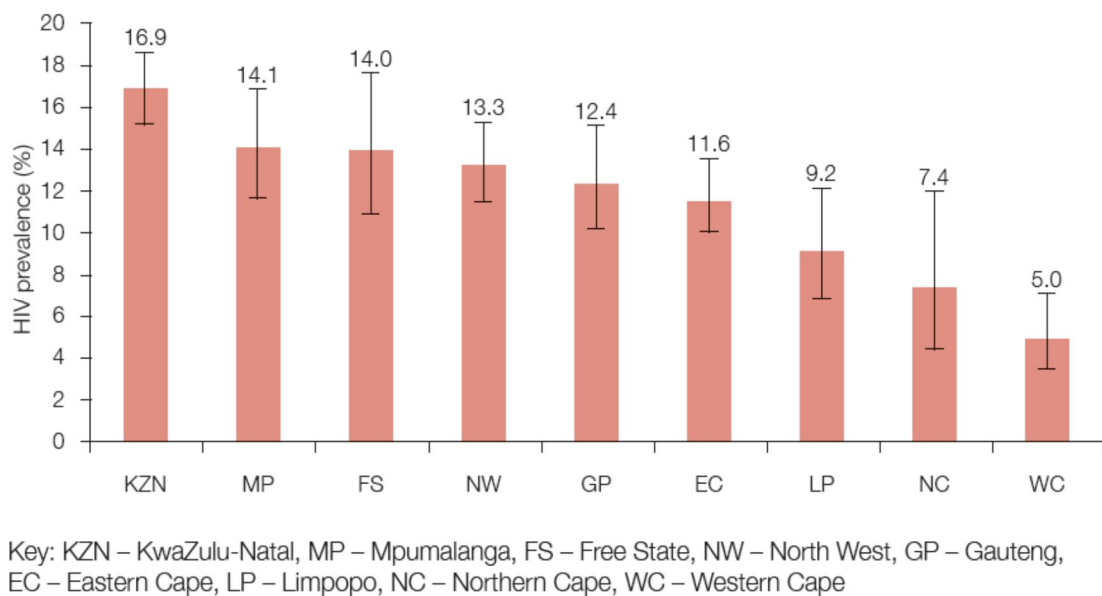


Figure 2: Overall HIV prevalence by province in South Africa (Shisana et al., 2014)

Although the epidemic in South Africa is generalised, certain groups have been identified as at increased risk for HIV infection including people living in informal settlements, young women, recreational drug users, disabled persons (Shisana et al., 2014), men who have sex with men (MSM) (Lane et al., 2011), and sex workers and their clients (Ramjee & Gouws, 2002; Rees, Beksinska, Dickson-Tetteh, Ballard & Htun, 2000; van Loggerenberg et al., 2008).

South Africa has the largest ART rollout programme in the world and has made impressive progress in terms of ART coverage. In 2012, adult HIV treatment coverage was 81% (UNAIDS, 2013), with 1.9 million people on triple ART (Motsoaledi, 2012). Expanding access to ART has resulted in decreases in HIV-related adult mortality (Evans, 2013) and life expectancy has increased from 54 years in 2005 to 60 years in 2011 (Bradshaw, Dorrington & Laubscher, 2012). In addition, the country has made significant progress in terms of reducing mother-to-child transmission of HIV (Pillay & Barron, 2014). Despite these remarkable achievements, the number of new infections globally supersedes the number of persons on ART (UNAIDS/WHO, 2012). Further, South Africa has faced numerous crises in the rollout of ART (Bateman, 2013). A survey conducted between September and October 2013 found that one in five South African health facilities reported stock outs of ART in the preceding three months (Stop Stock Outs Project, 2013). Moreover, the alarming rate of new infections in the country, and trends of increased HIV risk behaviour, underscore the urgent need to intensify prevention efforts (Shisana et al., 2014) and develop increased options for HIV prevention (Merson, O'Malley, Serwadda, & Apisuk, 2008).

3. HIV prevention research

Given the devastating impact of the HIV epidemic over the last three decades, it is evident that the optimal approach to controlling new HIV infections is via multiple prevention strategies. To this end, several strategies for HIV prevention are currently being developed and tested, including microbicides, vaccines, index partner treatment, antiretroviral pre-exposure prophylaxis (PrEP) and drug substitution therapy for people who inject drugs (UNAIDS/WHO, 2012). Most of these HIV prevention strategies address sexual transmission of HIV, which accounts for the vast majority of new infections (Lagakos & Gable, 2008), particularly in Africa. Given the profound impact and burden of HIV, South Africa has become a hub for HIV prevention research, including trials of HIV vaccines, microbicides, PrEP and male circumcision. Further, South Africa has identified the prevention of new HIV infections as a key priority in its National Strategic Plan on HIV, STIs and TB (NSP) 2012-2016 (SANAC, 2011).

4. The research problem

All HIV prevention trials enrol HIV-uninfected participants, and in late-phase efficacy trials, participants are at high risk for HIV infection. The ethical obligation to protect the welfare of trial participants entails that they should be provided with access to an HIV prevention

package to help them remain HIV-uninfected. At a minimum, this package generally includes risk-reduction counselling, condoms, and testing and treatment for sexually transmitted infections (STIs), with some trials providing other additional interventions (McGrory, Philpott, Hankins, Paxton & Heise, 2010). The HIV risk-reduction interventions offered to participants in HIV prevention trials have traditionally been subsumed under the broad umbrella term of ‘standard of care’ (Heise, Shapiro & West Slevin, 2008), but have more recently been termed ‘the standard of prevention’ (cf. UNAIDS/WHO, 2012). Standards of prevention refer to the prevention package provided to all participants in a trial to lower their risk of HIV infection (Haire et al., 2013; Rennie & Sugarman, 2010). Within the context of biomedical prevention trials, this new ethical concept is already controversial (Macklin, 2008).

Efficacy trials of biomedical HIV prevention products are often conducted among high incidence populations, who are also most likely to benefit from effective prevention interventions (UNAIDS/WHO, 2012). Such trials are funded by high-income countries but typically conducted in resource-constrained contexts which are often characterised by poor access to healthcare services (UNAIDS/WHO, 2012). Such disparities in resources have fuelled much debate about sponsor/investigator obligations to protect the welfare of trial participants by keeping them HIV-uninfected (Moorhouse, Slack, Quayle, Essack & Lindegger, 2014). The standard of prevention is a prominent ethical concern in HIV prevention trials (Macklin, 2009) and has become a recent topic of intense debate and consultation (cf. GCM, 2007; Haire, 2013; Macklin, 2008; McGrory et al., 2010; Philpott et al., 2011).

Given the unique ethical complexities in HIV prevention trials, specific guidelines have been developed to guide HIV prevention research in South Africa (MRC, 2003) and internationally (HPTN, 2009; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). However, standard of prevention norms in these guidelines are contentious (Essack, Slack, Koen & Gray, 2010; Philpott et al., 2011), with different guidelines proposing different normative standards (Haire, 2013).

There is debate about the practical feasibility of standard of prevention norms in ethics guidelines. Current ethics guidelines assert that participants should be provided with access to ‘optimal’ (MRC, 2003) or ‘state-of-the-art’ (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012)

HIV risk-reduction interventions. However, some contend that the state-of-the-art standard may be too aspirational and not practically feasible (HPTN, 2009; Macklin, 2009) especially in resource-constrained contexts with limited access to high quality prevention modalities (Macklin, 2010).

The ethical rationale underpinning the provision of HIV prevention services to participants is not settled. Some have argued that, given the experimental nature of HIV vaccine trials (HVTs), the fact that some participants receive placebo, and that HIV is incurable, researchers are ethically required to help participants remain HIV-negative by providing them with proven HIV preventive methods (Essack, Slack, et al., 2010; IAVI, 2007). Current ethics guidelines for biomedical HIV prevention trials (UNAIDS/WHO, 2012) assert that beneficence and non-maleficence support the obligation to provide prevention interventions to participants. Still, others have described reciprocal justice (Heise & Wood, 2005; McGrory et al., 2010), the therapeutic misconception and clinical equipoise, behavioural disinhibition, standards of care, and the duty of rescue as justifying the provision of a standard of prevention (McGrory et al., 2010).

There is little clarity about how decisions should be made about the standard of prevention in trials (cf. GCM, 2007; Macklin, 2008; McGrory et al., 2010), including when to add new effective prevention interventions to the standard package of prevention (e.g., Cowan & Macklin, 2014; GCM, 2007; Philpott et al., 2011). These decisions are complicated by many factors including that there are no set standards for making decisions, with variable standards apparently being used across trials and stakeholder groups (cf. Essack, Slack, et al., 2010; McGrory et al., 2010; Philpott et al., 2011). Therefore, there have been calls for the documentation of decision-making practices in HVTs (Essack, Slack, et al., 2010).

There has been debate about which prevention methods should be included in the prevention package (Macklin, 2008). While there is broad agreement that participants should receive access to certain HIV risk-reduction interventions (such as condoms, counselling and STI treatment), there has been some disagreement about obligations to ensure access to other interventions such as voluntary medical male circumcision (VMMC) (cf. Lie, Emanuel & Grady, 2006), post-exposure prophylaxis (PEP) (UNAIDS, 2000) and PrEP (McEneaney, 2012). There are also concerns that offering enhanced standard of prevention packages to all participants in HIV prevention trials may severely constrain the ability to obtain meaningful

results in trials (Macklin, 2008). Particularly, a high standard of prevention may lower HIV incidence and result in trial futility. Therefore, efforts to explore the threshold at which enhancing the standard of prevention would invalidate trials is both ethically and scientifically imperative (Essack, Slack, et al., 2010). Other objections to a state-of-the-art standard of prevention include that it may introduce significant inequities between trial participants and communities, and may result in undue inducement and increased behavioural disinhibition (HPTN, 2009).

Another complexity relates to who should pay for the provision of these HIV prevention interventions. Commentators have argued that the burden should not fall on sponsors and researchers alone; nor is it affordable for poorly resourced governments on their own (Macklin, 2008). One suggestion is that these costs be incorporated into budgets supported via public-private partnerships and that skilled negotiators be utilised in brokering such arrangements (Macklin, 2008). Ethics guidelines too, suggest that researchers and sponsors should collaborate with host country governments to ensure access to the highest standards of prevention and care (UNAIDS/WHO, 2012).

5. The research questions

There is increasing acknowledgement of the value of empirical research in bioethics. Empirical research can help describe facts to inform normative arguments, enable critical reflection on ethical norms (Kon, 2009a), identify the ethical challenges experienced in practice, ascertain whether ethical concerns have cultural nuances (Essack, Koen, et al., 2010) and/or provide information that may facilitate the improvement of ethical recommendations (Carter, 2009; Essack, Koen, et al., 2010).

There is little existing data on whether ethics recommendations are being implemented in HVTs, nor on the complexities faced by trial implementers. Recent research found that stakeholders perceived prevention norms in ethics guidelines as more controversial than care norms, especially regarding the extent to which they can be implemented (Moorhouse et al., 2014). Further, commentators have called for an exploration of 'the prevention services offered to HVT participants' (Essack, Slack, et al., 2010, p. 46) and an assessment of the extent to which actual practices (what *is* happening) correspond with ethics guidance (what *ought* to be happening according to norms) (Macklin, 2010). Such empirical data could respond to the criticism that ethics guidelines represent ideals that cannot realistically be

achieved in practice (c.f. Macklin, 2010), document actual practices in HVTs, including regarding decision-making (Essack, Slack, et al., 2010), provide an in-depth understanding of stakeholder reservations about selected ethics guideline recommendations (Moorhouse et al., 2014), and gauge the extent to which enhanced standards of prevention are worrying to researchers (cf. Macklin, 2008). Further, ethics principles should be informed by how the ground realities and empirical data can contribute to understanding how successfully ethics aspirations are operationalised in practice (Heise et al., 2008).

To this end, the present study, funded by the Wellcome Trust (Developing Country Projects Grant in Biomedical Ethics), aimed to explore 1) the extent to which standard of prevention decision-making and implementation practices at South African HVT sites resonate with related recommendations in ethics guidelines; 2) whether ethics guidelines address the concerns of key stakeholders about standards of prevention; and 3) the perspectives of HVT stakeholders on evolving standards of prevention and selected standard of prevention norms in ethics guidelines.

6. Scope of the thesis

This thesis uses empirical data to inform the debate on standards of prevention. It explores standard of prevention practices at five South African HVT sites (cf. Essack, Slack, et al., 2010); examines whether norms are implementable in practice (cf. Macklin, 2010) and whether guidelines anticipate how the ground complexities. It also explores stakeholders' perspectives on evolving standards of prevention (cf. Macklin, 2008) and selected standard of prevention norms in ethics guidelines (cf. Moorhouse et al., 2014).

These focused aims and objectives limit the ability of this thesis to comprehensively address all the complexities with standards of prevention in HVTs. This study focuses on HVTs conducted in South Africa only, and exclusively explores HIV prevention practices rather than reproductive healthcare services more broadly.

This study is framed within the social sciences. While it is hoped that data from this study will usefully inform the debate on standards of prevention, this study does not provide a normative philosophical analysis of standards of prevention. Empirical data are less relevant to questions about whether trial participants should receive prevention interventions, on what ethical grounds, and what standard of prevention is owed to trial participants and by whom.

Such questions are better suited to normative analyses. Further, given its qualitative approach this study does not define the threshold at which adding new tools to the prevention package will invalidate trials (cf. Essack, Slack, et al., 2010).

7. Overview of the thesis

Part one (Chapters 1-2) aims to provide an overview of the research problem and situate the study by describing the context within which HVTs are conducted. Chapter 2 offers an overview of HIV prevention research, with a focus on biomedical prevention interventions. A brief situational analysis of the South African HIV prevention trial landscape and the public healthcare system is undertaken. The chapter concludes by briefly documenting the major ethical issues that may arise when conducting prevention trials in South Africa.

Part two of this thesis (Chapters 3-5) focuses on normative/theoretical issues. In chapter three, ethics guidelines relevant to HVTs are reviewed to identify standard of prevention norms. These guidelines are also critically evaluated and compared in terms of standard of prevention recommendations. The relevant norms identified in this chapter are compared with actual standard of prevention practices documented through the empirical research undertaken in this study. In this conceptual review, several complexities with ethics recommendations on standards of prevention are identified. In chapter four, frameworks and criteria for making standard of prevention decisions are presented and critically reviewed. A three-step framework (Jay, Mayer, Burris, Gray & McGowan, n.d., unpublished manuscript) provides operational guidance for the enhancement of the prevention package as do criteria for decision-making developed at a consultation on standards of prevention (McGrory et al., 2010; Philpott et al., 2011). The good research governance model (Tarantola et al., 2007) spells out a process for operationalising stakeholder consultations that are recommended in guidelines for standard of prevention deliberations. Chapter 5 provides a detailed overview of the literature expanding on the current debates regarding standards of prevention outlined in the present chapter. Objections to providing a state-of-the-art standard of prevention to trial participants are also considered and previous empirical studies on standards of prevention are reviewed.

Part three (Chapters 6-11) of this study relates to the empirical component. In chapter six, details of the research methodology are provided, and the specific research questions and aims of the study are outlined. Empirical approaches to bioethics are justified and briefly

described, followed by a description of the research design, methodology and the philosophical underpinnings of this study. The sampling, data collection and data analysis procedures are presented and the rationale for adopting particular approaches explained. Considerations pertaining ethics are also discussed.

In chapter seven, empirical findings on standard of prevention decision-making are presented. Stakeholder perspectives on the ethical rationale for providing prevention services to trial participants are described. Standard of prevention decision-making practices and perspectives are presented according to the various stages at which decisions are made, namely protocol development, protocol review and protocol implementation. Chapter 8 presents stakeholder practices and perspectives regarding the evolving standard of prevention, and focuses on the criteria respondents considered relevant when making decisions on the enhancement of the prevention package. Chapter 9 presents the HIV prevention interventions provided in two HVTs at five South African HVT sites. It describes -what- prevention interventions were provided, to -whom- (participants, volunteers at screening, participants' partners or the wider community) and -how- (implementation practices). Stakeholder perspectives on challenges and complexities are also presented. Chapter 10 focuses on respondents' perspectives on selected (and controversial) standard of prevention norms in ethics guidelines and details some of the challenges experienced with operationalising ethics recommendation in HVTs. In Chapters 8-10, actual practices and reported complexities are compared with related recommendations in ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011, UNAIDS/WHO, 2012) and relevant literature.

Chapter 11 attempts to identify and relate the underlying ideas or assumptions (latent themes) in respondents' reports of their practices and perspectives on standards of prevention to the literature and normative framework. This chapter aims to move beyond a descriptive analysis of the results by offering an explanation and interpretation of the study's key findings. It considers the limitations of the study and the role of the researcher in the research process (reflexivity).

Chapter 12 concludes this thesis by reiterating the main study findings and drawing conclusions. It provides recommendations for future research, strengthened practices, more responsive guidelines, and for stakeholder capacity building.

CHAPTER 2

CONTEXTUALISING HIV VACCINE TRIALS IN SOUTH AFRICA

This chapter aims to provide an overview of the HIV prevention research process, with a focus on biomedical HIV prevention interventions. It provides a historical overview of the South African HVT landscape and public healthcare system. The chapter concludes by briefly documenting some of the research undertaken in South Africa on the ethical issues that may arise when conducting HVTs in developing country contexts.

1. The HIV prevention response

HIV was first reported in the United States (US) in June 1981 among homosexual men. In South Africa, the first case of HIV was reported in 1982 (Abdool Karim & Abdool Karim, 2002) and in its early years, HIV was limited to the white homosexual population. During the country's transition to a democratic state, it emerged as the epicentre of the global HIV/AIDS epidemic, primarily because of sexual transmission among the black African heterosexual population (Rohleder, Swartz, Kalichman & Simbayi, 2009). Given the rapid pace at which the HIV prevalence increased, the spread of HIV was considered 'explosive' (Abdool Karim & Abdool Karim, 2002).

In response, by the mid-1980s, community groups were established in many countries to provide care and support to those infected and to develop and promote HIV prevention strategies (Merson et al., 2008). History has demonstrated that vaccines are the most effective method to eradicate global viral epidemics (Bekker, Beyrer & Quinn, 2012; Morris, Williamson, Mlisana & Gray, 2009). However, the initial hope that the discovery of an effective HIV vaccine would be imminent proved unfounded (Esparza, 2013). Experience now indicates that the path to an effective prophylactic HIV vaccine is lengthy and complicated (Barouch, 2008; Morris et al., 2009).

Much research has been conducted on the determinants of HIV and it is increasingly accepted that to be effective, HIV prevention should incorporate behavioural, biomedical, and structural interventions or a combination prevention approach (Bekker et al., 2012; Hankins & de Zaluendo, 2010; Rotheram-Borus, Swendeman & Chovnick, 2008). As promising HIV prevention interventions become available, each new HIV prevention technology will

become an important additional tool for those at risk of HIV infection, hopefully approximating the way in which an expanded array of contraceptive options has increased their overall use (Merson et al., 2008, p. 486).

2. Testing HIV prevention interventions

As outlined above, HIV prevention interventions target behavioural, biomedical and structural HIV risk factors (Vermund, Allen & Abdool Karim, 2009). While some interventions were evaluated in randomised controlled trials (RCTs) with HIV as the endpoint, for some interventions where RCTs were not feasible, effectiveness was estimated through observational studies and quasi-experimental research (Vermund et al., 2009).

All biomedical HIV prevention interventions are evaluated in a stepwise manner over various stages. After initial laboratory testing and animal studies to establish safety, products are tested in clinical trials with human participants (Interagency Coalition on AIDS and Development (ICAD), 2010; SAAVI, n.d.). Prior to human trials, national regulatory authorities like the South African Medicines Control Council (the MCC), and international/national/local research ethics committees (RECs) must approve clinical trial protocols to ensure that trials are conducted both scientifically and ethically (ICAD, 2010; NHA, 2003). Products with approved protocols proceed to phase I trials, which enrol a small number of low-risk participants to evaluate safety. Phase II trials enrol larger numbers of low- and high-risk participants to gather extended safety data and in the case of vaccines, data on the human immune response. Phase IIB or 'proof of concept' trials are designed to bridge the gap between phase II and phase III trials (Geise & Duerr, 2009) by providing information on the potential efficacy of the intervention and testing whether the candidate intervention warrants moving into larger efficacy studies. Such trials are less costly in terms of time, money and sample size but do not provide sufficient information for regulatory approval. Phase III trials are required to develop a useable and licensable HIV prevention strategy (UNAIDS/WHO, 2012) and enrol thousands of high-risk participants to establish whether the experimental product prevents HIV infection, and delays the onset of AIDS disease in the case of vaccines.

Prophylactic HVTs involve healthy, HIV-uninfected participants. In these randomised, double-blinded, placebo-controlled trials, participants are randomly assigned to receive the experimental vaccine or placebo. HIV vaccine efficacy studies are conducted to determine

whether the experimental vaccine can decrease the risk of HIV infection more than the standard prevention package provided to participants in both arms of the study (cf. de Zoysa, Elias & Bentley, 1998). Clinical trials are overseen by data and safety monitoring boards (DSMBs) who monitor unblinded trial results at regular intervals to determine whether the experimental product is safe, effective, or whether the trial can no longer answer the questions it was designed to answer (Armstrong & Furberg, 1995).

To measure the efficacy or effectiveness of an HIV prevention intervention, efficacy trials usually use proxy or surrogate markers that are predictive of the clinical endpoint. For example, in HIV treatment trials, viral suppression is used as a surrogate marker for clinical progression (Lagakos & Gable, 2008). However, in HIV prevention trials validated surrogate markers for HIV infection or product activity have yet to be identified (Lagakos & Gable, 2008; McCormack, Gafos, Desai & Cohen, 2014; Richert et al., 2014). Therefore, the primary endpoint in HIV prevention trials is HIV infection. This ‘prevention paradox’ (Sugarman & Grace, 2010), which requires that participants contract HIV in order to determine the effectiveness of an HIV prevention intervention is one of the enduring ethical complexities in HIV prevention research. The size and statistical power of the trial is determined by the number of HIV infections that occur in the trial population (Richert et al., 2014). In order to have sufficient power to evaluate efficacy, trials need to be conducted in contexts with a relatively high HIV incidence rate (Rida & Lawrence, 1994). However, in comparison to other disease outcomes, HIV infection is relatively rare even among high-risk groups. Therefore, in order to be feasible, HIV prevention efficacy trials enrol large numbers of participants (typically between 1000-4000) at one site or across multiple sites, in communities with an annual HIV incidence rate of at least 3-4%, and follow them up for several years (Lagakos & Gable, 2008).

A comprehensive overview of all available and potential HIV prevention interventions is beyond the scope of this thesis. The following section focuses primarily on biomedical HIV prevention interventions, with some consideration of behavioural (counselling) approaches.

2.1 Risk-reduction counselling

Providing trial volunteers with education and counselling on how they can reduce their risk and protect themselves from HIV infection is a key component of HVTs (IAVI, 2005).

However, in many of the countries where clinical trials of prevention interventions are being

conducted, the efficacy of behavioural risk-reduction strategies is yet to be proven (IAVI, 2005; Lagakos & Gable, 2008). While some studies suggest that behavioural risk-reduction interventions are effective in reducing risk behaviours (IAVI, 2005) there are no studies demonstrating significant reduction in HIV infection rates (Lagakos & Gable, 2008). In a review of nine RCTs that tested five behavioural interventions, Ross (2010) reported that while some of these interventions had an impact on STIs, none of these trials demonstrated a significant reduction in HIV incidence. The only behavioural intervention study with an HIV infection endpoint (Project EXPLORE), found no effect of counselling on HIV acquisition (Bekker et al., 2012). However, risk-reduction counselling is argued to be invaluable for enhancing knowledge of HIV/STIs, enhancing skills for condom use, increasing the effectiveness of biomedical interventions (Lagakos & Gable, 2008) and minimising risk-compensation when introducing partially effective technologies (Hankins & de Zaluendo, 2010).

2.2 Male and female condoms

Evidence of the effectiveness of male condoms in preventing HIV infection has been increasing since the recommendation of their use in the early 1980s (Padian, Buvé, Balkus, Serwadda & Cates Jr, 2008). Male condoms are considered one of the cornerstones of HIV prevention programming (Rotheram-Borus et al., 2009). Condom use is recommended particularly for individuals with multiple partners, whose primary partner is HIV-infected or whose partner's sero-status is unknown (Surgeon General, 1993, in Weller & Davis, 2002). The degree of protection conferred by condoms is unknown due to complexities which make the RCT an unethical design to test their effectiveness (Weller & Davis, 2002). However, the effectiveness of male condoms has been estimated at approximately 80%, based on data from longitudinal cohort studies with serodiscordant couples (Weller & Davis, 2002) and can be as high as 95% when used consistently (Pinkerton & Abramson, 1997).

Female condoms have been evaluated in STI prevention efficacy trials but no trials have directly examined their effectiveness in preventing HIV (Padian et al. 2008). Female condoms have been estimated to be highly effective in reducing risk of HIV infection (Padian et al., 2008) and research has shown that when used correctly and consistently, they are as effective as male condoms (Vijayakumar, Mabude, Smit, Beksinska & Lurie, 2006). However, uptake of the female condom is low, partly due to its 'inconspicuous presence', lack of availability and high cost (Padian et al., 2008).

2.3 STI Treatment

STIs increase the risk of sexual transmission of HIV as indicated by evidence from multiple longitudinal studies (e.g., Røttingen, Cameron & Garnett, 2001). For this reason, the prompt diagnosis and treatment of STIs has been incorporated in HIV prevention programming (Bekker et al., 2012).

Of four community-based RCTs of the effectiveness of syndromic STI treatment in reducing HIV risk, only one was found effective (Gray & Wawer, 2007). However, these findings may suggest that treating bacterial STIs may be more effective in reducing HIV incidence in contexts with a high prevalence of STIs and a high incidence of HIV (Bekker et al., 2012; Vermund et al., 2009).

Research also suggests that infection with herpes simplex virus type 2 (HSV-2), increases the risk of HIV transmission three-fold (Freeman et al., 2006). However, three RCTs found that suppressing HSV-2 with chronic antivirals was ineffective in reducing the risk of HIV transmission (Hayes, Watson-Jones, Celum, van de Wijgert & Wasserheit, 2010). While biological evidence for STI treatment suggests it is potentially efficacious, trials have been challenged by several methodological complexities (Lagakos & Gable 2008).

2.4 HIV prevention for injection drug users (IDUs)

IDUs account for a fair proportion of global HIV infections (UNAIDS/WHO, 2012) and have been identified as at increased risk of infection in South Africa (Shisana et al., 2014). While RCTs of needle exchange programmes may not be feasible, access to sterile injecting equipment, drug treatment (substitution therapy) and behavioural risk-reduction counselling have been proven effective in preventing HIV acquisition among this sub-group (Valdiserri, Ogden, & McCray, 2003). However, the provision of equipment for people who inject has proven politically challenging in many contexts, because this has been seen (based on no empirical evidence) as discouraging injecting (Bekker et al., 2012, p. 16).

2.5 Voluntary medical male circumcision (VMMC)

Three trials conducted in South Africa, Kenya and Uganda, indicated that a man's risk of contracting HIV through heterosexual sex is at least halved if he is circumcised (Auvert et al., 2005; Bailey et al., 2007; Gray et al., 2007). The first RCT of male circumcision conducted in Orange Farm, South Africa was prematurely halted after an interim review of data revealed

that circumcision decreased chances of acquiring HIV by 60% (Auvert et al., 2005). Two additional studies which were conducted in Kenya and Uganda to assess the applicability of the South African findings across contexts, were stopped after interim data suggested that medically performed circumcision decreased a man's risk of being infected with HIV from women by 53% and 48% respectively (Bailey et al. 2007; Gray et al. 2007). In reviewing this evidence, WHO/UNAIDS (2007, p. 3) recommended that VMMC be recognized as an additional, important strategy for the prevention of heterosexually acquired HIV infection in men.

2.6 Topical microbicides

Microbicides are substances (gels, creams, suppositories and vaginal rings) designed to be applied to the vagina to prevent HIV infection and other STIs. Several large-scale trials of first generation microbicides were conducted, all producing disappointing results (Padian et al., 2008; Vermund et al., 2009). In response, second-generation microbicides have included topical applications of antiretroviral agents (Klasse, Shattock & Moore, 2008; Padian et al., 2008), and have started to produce some promising results (see CAPRISA 004 trial results described in 2.8 below).

2.7 Post-exposure prophylaxis (PEP)

Given that ART is effective in reducing HIV viral loads by suppressing viral replication, it may be effectively used as a preventive method prior to, or after exposure to HIV, and ART is now routinely used after occupational exposures in healthcare settings (cf. Young, Arens, Kennedy, Laurie & Rutherford, 2007). There is no conclusive evidence of the effectiveness of ART in preventing HIV acquisition after sexual exposure but data from animal studies have suggested that a "window of opportunity" may exist in which ART could suppress viral replication and prevent HIV infection following the initial exposure (Kim, Martin & Denny, 2003, p. 102). Guidelines in many countries, including South Africa, also recommend PEP following potential sexual exposure to HIV (Venter, 2008).

2.8 Pre-exposure prophylaxis (PrEP)

PrEP for HIV is the use of antiretroviral drugs to prevent HIV acquisition. The concept of using treatment as prevention has been proven successful in the prevention of mother-to-child transmission (PMTCT) of HIV (Hammer, 2011). Several RCTs of PrEP have been completed or are ongoing to evaluate its effectiveness in reducing HIV acquisition among HIV-

uninfected high-risk populations (Jiang et al., 2014), including IDUs, HIV serodiscordant couples, heterosexual men and women, and men and transgender women who have sex with men.

Daily oral PrEP has been found effective in four RCTs (iPrEx, PartnersøPrEP, Botswana TDF2 and the Bangkok Tenofovir Study) but not in the Fem-PrEP or VOICE trials (Tenofovir arm) (Cowan & Macklin, 2014; Hankins & Dybul, 2013; Jiang et al., 2014).

Tenofovir gel was proven effective in CAPRISA 004 (Abdool Karim et al., 2010) when used pericoitally but not in VOICE with daily use (Hankins & Dybul, 2013). The FACTS 001 trial, designed as a confirmatory trial for CAPRISA 004 and to provide evidence for the regulatory approval of Tenofovir gel, is currently underway (Abdool Karim, Baxter & Abdool Karim, 2013). A recent meta-analysis found that òPrEP is associated with a reduced risk of HIV infection in high risk populationsö (Jiang et al., 2014, p. 4).

2.9 Treatment as prevention

A study conducted with serodiscordant couples tested the impact of earlier access to ART for the HIV-infected partner on HIV transmission. The study was conducted with couples across multiple sites and countries, including South Africa. Findings indicated a very high protective effect of 96% (Cohen et al., 2011).

2.10 Vaccines

The development of a safe and effective HIV vaccine remains one of the greatest hopes for abating the HIV epidemic (Fauci, 2008). HIV vaccines can be either preventative or therapeutic. Preventative (or prophylactic) HIV vaccines are tested on HIV-negative participants and aim to prevent HIV infection or delay progression to AIDS disease in those participants who become HIV-infected (SAAVI, n.d.). Therapeutic vaccines are tested only in HIV-positive participants with the aim of determining whether the vaccine strengthens the immune response to HIV (SAAVI, n.d.). Most vaccines currently tested in clinical trials are preventative vaccines (the focus of this study).

The first phase I trial of an HIV vaccine was conducted in 1987, and since then more than 200 early-phase clinical trials have been conducted (Esparza, 2013). However, while over 50 candidates have been tested in phase I trials, only about 20 have moved into phase II studies

and by 2011 only five had progressed to phase IIB/III clinical efficacy trials (Geise & Duerr, 2009).

Initiated in the mid-1990s, the first vaccine candidate to undergo phase III testing was AIDSVAX, which comprised two separate studies sponsored by VaxGen. One trial enrolled approximately 5,400 participants, mainly MSM in North America and the Netherlands, and the second involved around 2,500 IDUs in Thailand (Geise & Duerr, 2009). The vaccine was made from a single HIV protein and was meant to stimulate a protective antibody response. However, no protective effect was found in either trial (Esparza, 2013). Although the trials had disappointing results, they demonstrated that large-scale HIV trials could be conducted safely and successfully in a variety of settings (Geise & Duerr, 2009).

The second trials were two phase IIB trials of the Merck Adenovirus-5 (Ad5) based vaccine candidate. The STEP Study (or HVTN 502) enrolled 3000 high-risk individuals from the Americas, Caribbean and Australia and included homosexual men who had multiple partners or who practiced unprotected anal intercourse, and high-risk heterosexual men and women (Gray, Buchbinder & Duerr, 2010). A second trial of the same vaccine, HVTN 503 or Phambili, was conducted in South Africa and began enrolment in January 2007. An interim analysis of STEP trial data in September 2007 found that the vaccine would not meet its efficacy endpoints and further vaccinations were halted. The DSMB for the South African trial decided to discontinue immunisations and enrolments based on data from the STEP study, which showed that in addition to not meeting study endpoints, there was a trend towards increased risk of HIV infection among a subgroup of vaccinees (Gray et al., 2010).

In 2009, results of the largest trial to date, the Thai prime-boost phase IIB vaccine trial (RV144) sponsored by the National Institutes of Health (NIH), the US military, and the Thai Ministry of Health, and which enrolled over 16000 Thai men and women, were announced. Results showed that the vaccine reduced HIV by 31.2% among vaccinated participants compared with those who received the placebo (Rerks-Ngarm et al., 2009). While the effect was modest, these results have demonstrated that a vaccine can protect against HIV (Rerks-Ngarm et al., 2009) and there are plans to conduct confirmatory trials in other populations, including South Africa (Esparza, 2013).

The HVTN 505 phase IIB prime boost trial was prematurely closed in April 2013, after an interim analysis by the DSMB revealed that the vaccine was not effective in reducing HIV acquisition or viral load (Esparza, 2013; Nageswara Rao, 2014).

The Pox-Protein Public-Private Partnership (P5)¹ was established in 2010 to build on the results of the RV144 trial. To this end, a phase I trial (HVTN 097) testing the RV144 regimen commenced in South Africa in June 2013, with further phase II and III trials planned for 2015 that are hoped to result in licensure of an ALVAC protein prime boost vaccine (similar to RV144). The efficacy trial (HVTN 702) is expected to enrol over 5000 participants in late 2016 (HIV Vaccines and Microbicides Resource Tracking Working Group (RTWG), 2014). The HVTN is also planning to test different pox-protein combinations in phase I and II trials in Southern Africa, anticipated to commence in 2015.

3. The South African HIV vaccine trial landscape

HIV prevention research is a global undertaking. For scientific and statistical reasons, efficacy trials of HIV prevention interventions are conducted amongst populations with a high incidence of HIV infection, often in developing country contexts (de Zoysa et al., 1998; Esparza & Bhamarapravati, 2000). South Africa is ideally positioned to conduct large-scale HIV prevention trials given its scientific capacity, good infrastructure, high HIV incidence rates (Morris et al., 2009; Ramjee et al., 2010) and commitment to a human rights culture (Delany-Moretlwe, Stadler, Mayaud & Rees, 2011). Actually, most phase II and phase III trials are conducted in Southern Africa and Southeast Asia because of high HIV incidence and because it is socially valuable to conduct research in those countries where prevention tools are needed the most. This also ensures product acceptability among those populations most likely to benefit from effective interventions (ICAD, 2010). Of 669, 224 trial participants enrolled in HIV prevention trials globally in 2013, 510,689 were enrolled in Africa, with Southeast Asia a distant second at 76,192 (RTWG, 2014). South Africa has become a hub for HIV prevention research and to date, several biomedical trials of HIV prevention technologies have been undertaken in South Africa, including VMMC (Auvert et al., 2005), vaccines (e.g., Gray et al., 2010), microbicides (e.g., Abdool Karim et al., 2010; Ramjee, Govinden, Morar & Mbewu, 2007), PrEP (e.g., Grant et al., 2010), PMTCT (Petra

¹ <http://www.vaccineenterprise.org/content/P5Partnership>

Study Team, 2002), treatment as prevention (Cohen et al., 2011), and the vaginal diaphragm (Padian et al., 2007).

The South African AIDS Vaccine Initiative (SAAVI)², a lead programme of the Medical Research Council (MRC), was established in 1999 with the mandate to coordinate the research, development and testing of safe and effective HIV vaccines in South Africa (MRC, 2003). SAAVI received funding from the South African government through the Department of Health (DoH), the Department of Science and Technology, Eskom, the International AIDS Vaccine Initiative³ (IAVI), the NIH⁴ (MRC, 2003), and more recently the Italian government. There are six HVT units with various sites across South Africa, namely 1) Perinatal HIV Research Unit (PHRU: Soweto); 2) Desmond Tutu HIV Centre (DTHC: Cape Town); 3) Centre for the AIDS Programme of Research in South Africa (CAPRISA: Durban); 4) Aurum Institute (Klerksdorp, Orkney, Stilfontein, and Hartebeesfontein (KOSH)); 5) Medunsa Clinical Research Unit (MeCRU: Medunsa); and 6) Walter Sisulu University AIDS Vaccine Research Unit (Mthatha). To date, PHRU, DTHC, CAPRISA, KOSH and Medunsa have conducted clinical trials of HIV vaccines while the Walter Sisulu site is being developed to conduct trials in future. These sites have conducted various HVTs with funding from IAVI, SAAVI and/or the HIV Vaccine Trials Network⁵ (HVTN). IAVI is a global not-for-profit, public-private partnership working to accelerate the development of preventative HIV vaccines. Four of these sites, beside Walter Sisulu and Medunsa, are part of HVTN HIV vaccine trials units (or HVTUs) consisting of a global network of medical research institutions where experimental HIV vaccines are tested (HVTN, n.d.). HVTN is the world's largest publicly-funded international collaboration focused on the development of vaccines to prevent HIV/AIDS (HVTN, n.d.). HVTN is supported through a cooperative agreement with the National Institute of Allergy and Infectious Diseases (NIAID), which is a component of the NIH (HVTN, n.d.). There are plans to expand site capacity in South Africa as it prepares to conduct two large-scale licensure trials.

South African trial centres have sites over various locales, both rural and urban, some of which are nationally and internationally recognised as leaders in HIV prevention research.

² <http://www.saavi.org.za/>

³ <https://www.iavi.org/>

⁴ <http://www.nih.gov/>

⁵ <http://www.hvtn.org/en.html>

Sites have the benefit of being in close proximity to hospitals, primary healthcare clinics and government treatment centres. In South Africa, HIV infection risk is correlated with other structural risk factors, including poverty, social marginalisation, unemployment, and inadequate access to formal housing, education and healthcare services (Shisana et al., 2014). Most of the trial sites are located in communities that are particularly vulnerable to many of these structural risks.

The first HVT conducted in South Africa in 2003 was a phase I trial of the of the AlphaVax replicon Vector clade C vaccine candidate. The trial, conducted by the HVTN, enrolled 48 participants at two clinical trial sites in South Africa, namely, the PHRU and the SAAVI Vaccine Research Unit at the MRC in Durban. Subsequently several additional preventative vaccine trials of various phases have been conducted. The funding for these trials was largely from networks like HVTN and IAVI, with the candidate vaccine often supplied by pharmaceutical companies (Essack, Koen et al., 2010).

The South African context however, presents some unique challenges for HIV prevention research. Firstly, host communities might be very distrusting of research given historical abuses during apartheid under the guise of research (Baldwin-Ragaven, London & de Gruchy, 2000; Barsdorf & Wassenaar, 2005). In post-apartheid South Africa, such suspicion and mistrust is evident in the notion that the AIDS epidemic was conjured up by the apartheid government to eliminate the black population (Niehaus & Jonsson, 2005). This mistrust has been amplified by the premature closures of some trials because of increased risk of HIV infection in the product arm, namely, the Cellulose Sulphate microbicide trial and the Phambili HVT (Essack, Koen, Slack, Lindegger & Newman, 2012). The closure of the Cellulose Sulphate trial in particular, received negative and sensationalised media coverage, which created anxiety and mistrust among trial participants and the community (Ramjee et al., 2007). Therefore, in establishing and implementing HIV prevention trials in South Africa, researchers are required to build trust and address the historical stereotype of researchers as villains (Delany-Moretlwe et al., 2011, p. S8).

South Africa has a highly developed ethical-legal framework to regulate clinical trials. Apart from the Constitution, other relevant statutes are the National Health Act No. 61 of 2003 (NHA) and the Medicines and Related Substances Act No. 101 of 1965 (Andanda, 2010). All clinical trials with sites in South Africa must be registered with the DoH and reviewed by the

MCC, a statutory body that reviews all clinical trials and is tasked with the registration of new medicines or a change in product indication (Andanda, 2010).

South African law (NHA, 2003) requires that all health research in South Africa should be relevant to national health priorities, comply with obligations specified by the National Health Research Ethics Council (NHREC) and be submitted for ethics review (Strode, 2013) to a South African REC. The NHREC, established in terms of the National Health Act (2003), is responsible for the oversight and accreditation of South African RECs that review health research protocols (Moodley & Myer, 2007). All health research with human participants should obtain mandatory written informed consent, comply with prescribed norms, ensure that therapeutic research with minors is in their best interests and obtain consent from the minor's parents/legal guardians, from the minors if they have understanding, and, controversially (Strode, Slack, Wassenaar & Singh, 2007), the Minister of Health if the study is classified as "non-therapeutic". This legal framework has received some criticism including that it is overprotective of participants, stifles REC flexibility, and contradicts well-established ethical norms (Strode, 2013). However, compared to many developed and developing countries, South Africa has established a system of mandatory review to ensure that potentially harmful health research is less likely to be conducted. In comparison to the US for example, South Africa's framework for ethics review "is in many cases equivalent to the US institutional review board (IRB) and Office for Human Research Protections (OHRP) oversight system, is wider reaching, and has no exclusions" (Cleaton-Jones & Wassenaar, 2010, p. 710). Further, the regulatory and oversight system of non-federally funded research in the US for example, is less well regulated than South Africa (Cleaton-Jones & Wassenaar, 2010).

4. The healthcare system in South Africa

The right to health is enshrined in the South African constitution (Republic of South Africa, 1996). However, the healthcare system in South Africa has a challenging history. Historically healthcare, like all other facets of South African society, was racially disparate. The transition from apartheid to a democratic state came with significant health reforms, including the vision of universal access to primary healthcare (DoH, 1997) and the construction of new healthcare facilities.

Post-apartheid South Africa has prioritised free healthcare for all citizens and services are available at no cost at the primary healthcare level (Coovadia, Jewkes, Barron, Sanders & McIntyre, 2009). However, one of the major obstacles to the creation of an effective and efficient healthcare system has been the HIV/AIDS epidemic, which has reversed many of the initial gains made in public healthcare (Harrison, 2009). Chief among reasons for the explosive HIV epidemic in South Africa has been poor HIV/AIDS policies (Nattrass, 2008). During the transition to democracy AIDS denialism found its way into politics and policies in South Africa (Nattrass & Kalichman, 2009, p. 132). Despite immense public criticism (see Figure 3), the government under the leadership of former President Thabo Mbeki and Health Minister Dr Manto Tshabalala-Msimang, rejected AIDS science in favour of pseudoscience and resisted the rollout of ART (Nattrass & Kalichman, 2009). It has been estimated that this restriction of access to ART resulted in the premature death of over 330,000 people and 35,000 children being born HIV-positive (Chigwedere, Seage III, Gruskin, Lee & Essex 2008).

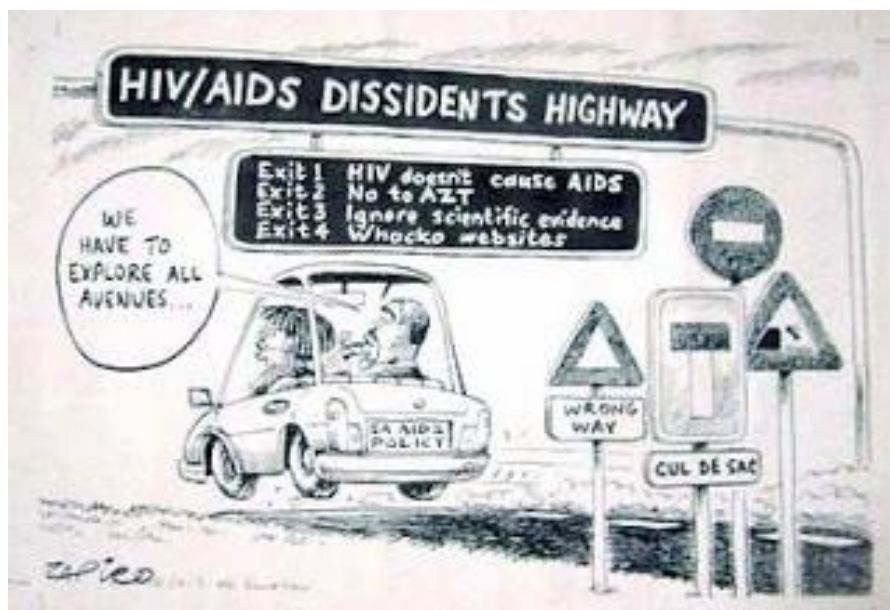


Figure 3: Popular South African cartoonist Zapiro on AIDS denialism in South Africa

Despite expansive health reform, apartheid continues to impact on health inequities to the extent that the current health system has been described as 'unequal and racially skewed' (Mayosi et al., 2012, p. 12). Research has indicated that in terms of access to healthcare, inequalities between better-resourced and poorer provinces remain (Stuckler, Basu & McKee, 2011). While primary healthcare services have become increasingly accessible, long

distances, time constraints and the cost of transportation impede access to secondary and tertiary facilities (Harris et al., 2011). Furthermore, racial, socio-economic, and rural-urban differentials in health outcomes, and between the public and private health sectors (Harris et al., 2011, p. S103) are pervasive. It is hoped that the introduction of National Health Insurance (NHI) may help reduce these inequities (Mayosi et al., 2012).

While the debilitating effects of AIDS denialism remain (Rohelder et al., 2009), the politics of HIV/AIDS have shifted radically in South Africa. Under the stewardship of Barbara Hogan and later Dr Aaron Motsoaledi in the Ministry of Health, government funding increased from R4.5 billion in 2009/10 to R8.4 billion in 2010/11 to accommodate expanded access to ART, HIV prevention, and PMTCT scale-up (Mayosi et al., 2012). This commitment is reflected in South Africa's current NSP, which specifies four primary strategic objectives, namely:

- 1) Addressing social and structural barriers that increase vulnerability to HIV, STI and TB infection;
- 2) Preventing new HIV, TB and STI infections;
- 3) Sustaining health and wellness; and
- 4) Increasing the protection of human rights and improving access to justice (SANAC, 2011, p. 9).

The NSP aims to reduce new HIV infections by at least 50%, using approaches that combine biomedical, behavioural and structural interventions (SANAC, 2011). There are plans to increase access to male and female condoms by 2016, for the scale-up of VMMC services (1.6 million circumcisions by 2016) and to ensure access to high-quality STI treatment. In addition, the NSP specifies the need to determine the feasibility of implementing new innovative biomedical strategies such as PEP, PrEP, microbicides and treatment as prevention (SANAC, 2011). While these objectives and strategies are commendable, the high rate of new infections reported in Chapter 1 (469, 000 in 2012) casts doubt about whether targets to reduce incidence by 50% are achievable.

4.1 HIV prevention services available in the public healthcare system

Preventing new HIV infections remains a priority for the South African government. The increase in government spending on HIV and AIDS programmes has also had positive impacts on South Africa's ability to implement and improve access to effective HIV prevention interventions. The South African public health sector implements a combination of HIV prevention interventions, including HIV counselling and testing, male and female

condom distribution, VMMC, and STI management, among others (DoH, 2013). Further, ARV prophylaxis (PEP) is offered in cases of sexual assault (DoH, 2013).

4.1.1 Access to HIV counselling and testing (HCT)

In March 2010, updated HCT guidelines were introduced. These guidelines revised counselling protocols and advocated a shift to voluntary provider-initiated HCT (DoH, 2010). In April 2010, an HCT campaign was launched and it is estimated that by June 2011, 13.4 million people had tested for HIV (Mbengashe, Nevhutalu, Chipimo, Chidarikire & Diseko, 2012), with 4500 public health facilities offering provider-initiated counselling and testing, and voluntary counselling and testing (VCT) (Peltzer & Matseke, 2013).

4.1.2 Access to condoms

The government-funded condom distribution programme has shown substantial growth over the years and in 2012/13 approximately 501,451,958 male condoms and 11,199,885 female condoms were distributed (DoH, 2013). However, this was below the targeted distribution rate, and the number of condoms distributed are insufficient to ensure consistently safer sexual acts (DoH, 2014). Further, the distribution of female condoms is substantially lower than male condoms. Stock outs and poor accessibility of female condoms have also been reported (DoH, 2014).

4.1.3 VMMC

Despite evidence from RCTs that VMMC is an effective HIV prevention strategy and its endorsement by normative bodies (UNAIDS and WHO) in 2007, South Africa only launched its ongoing campaign to promote and rollout VMMC in April 2010. VMMC is provided as part of integrated HIV prevention services at public health facilities, at standalone sites, at circumcision camps and using roving teams (DoH, 2014). It is estimated that 1,234,600 circumcisions were conducted from the launch of the campaign until August 2013, including approximately 329,000 circumcisions carried out by non-governmental organisations (NGOs) (Shisana et al., 2014). However, in provinces practicing traditional circumcisions (e.g., Eastern Cape, Mpumalanga and Limpopo), rates of uptake of VMMC have been low (Shisana et al., 2014).

4.1.4 Access to STI treatment

The prevention and timely treatment of STIs is a key public health imperative in South Africa. To this end, the STI syndromic management approach is an integrated component in primary healthcare clinics and available at no cost (Lewis & Maruma, 2009).

4.1.5 PEP

Public healthcare facilities only provide access to PEP for occupational exposures and in cases of penetrative sexual abuse or sexual assault (DoH, 2008). However, the Minister of Health, Dr Aaron Motsoaledi has recently discussed plans to develop a PEP programme (Maurice, 2014), which may provide PEP for all risky sexual exposures (cf. SANAC, 2011).

4.1.6 PrEP

The current NSP (SANAC, 2011) calls for the consideration of new modalities for HIV prevention, including PrEP. Some commentators have argued that populations at high-risk for HIV in South Africa should be offered PrEP, noting that PrEP is being offered in the private sector, but [that] no services exist in the state sector (Rebe & McIntyre, 2014, p. 11). Truvada is not currently licensed for use as PrEP in South Africa (Abdool Karim & Baxter, 2014). However, Southern African guidelines on PrEP have been developed in order to assist practitioners prescribing PrEP to MSM clients at risk for HIV (Bekker et al., 2012).

5. Ethical issues in South African HVTs

HVTs are often funded by sponsors from well-resourced contexts while the communities from which participants are recruited are often poor or marginalised, and may have limited access to education and healthcare services (Delany-Moretlwe et al., 2011; Miller et al., 2010; UNAIDS/WHO, 2012). Such disparities have framed tensions about sponsor-researcher obligations to participants in HVTs (Moorhouse et al., 2014). The ethics of research in developing countries is complex and has been extensively deliberated (Benatar, 2002; Emanuel, Wendler, Killen & Grady, 2004; Nama & Swartz, 2002; Shapiro & Meslin, 2001). In South Africa, there has been much consideration of the ethical issues that arise when conducting HVTs and other prevention trials (e.g., Moodley, 2002; 2007; Slack et al., 2000), including an exploration of stakeholder perspectives on ethical challenges in South African HVTs (Essack, Koen, et al., 2010). While a detailed review of all the literature is beyond the scope of this study, some of the research on ethical issues in South African HIV prevention trials, and especially in HVTs, is briefly documented below. This review is

clustered according to principles for conducting research in developing country contexts (Emanuel et al., 2004), where relevant.

There has been increasing emphasis on the value of community participation in research (MRC, 2003; Newman, 2006; Tindana, Singh, Tracy, Upshur & Daar, 2007) to the extent that specific guidelines on good participatory practice and stakeholder engagement (UNAIDS/AVAC, 2011) have been developed. Ensuring collaborative partnerships between stakeholders is also identified as an ethical principle for conducting research in developing countries (Emanuel et al., 2004). Studies have explored the potential contradictions between scientific imperatives for community participation (i.e., recruitment of participants) and community empowerment and participation (Swartz & Kagee, 2006). In South Africa and elsewhere, community advisory boards (CABs) are frequently used in HIV prevention research as a formal stakeholder advisory mechanism (UNAIDS/AVAC, 2011). To this end, their perspectives on ethical issues in HVTs have been sought (Essack, Koen, et al., 2010), the functions and operations of CABs in South African HVTs explored empirically (Reddy, Buchanan, Sifunda, James & Naidoo, 2010), and the extent to which they play meaningful roles in South African HVTs examined (Upton, 2011). As a pivotal stakeholder in HVTs, civil society organisations (CSOs) perspectives on stakeholder engagement in HIV prevention research have also been canvassed (Koen, Essack, Slack, Lindegger & Newman, 2013).

The fair selection of participants and communities (Emanuel et al., 2004) is pertinent in the South African context given historical research abuses during apartheid. Empirical research (Essack, Koen, et al., 2010) found concerns among South African stakeholders that certain groups were targeted for research, including that some participants may be selected because they are vulnerable. Given increasing concerns about the 'over-research' of particular communities, an in-depth empirical and ethical analysis of 'over-research' in communities was undertaken (Koen, 2010). There has also been intense focus on the ethics of research with vulnerable populations, for example, the enrolment of adolescents in HIV prevention trials (Bekker, Slack, Lee, Shah & Kapogiannis, 2014; Jaspan et al., 2010; McClure, Gray, Rybczyk, & Wright, 2004; Singh, Abdool Karim, Abdool Karim, Mlisana & Williamson, 2006; Strode, Slack, Grant & Mushariwa, 2005), the ethics of research with IDUs (Mamotte, 2012), and the ethical involvement of women in HVTs (Wassenaar & Barsdorf, 2007).

Ensuring that benefits of research are favourable in relation to risks (Emanuel et al., 2004) is an important ethical requirement of research. Several physiological risks of participation in HVTs have been described (Slack et al., 2000), including adverse reactions to the vaccine (Moodley, 2002) and vaccine-induced seropositivity. In addition, participation in HVTs may result in psychological risks (Slack et al., 2000) and social harm. Milford, Barsdorf and Kafaar (2007) described the potential social harms that may be experienced in South African HVTs. More recently, Stadler, Delany-Moretlwe, Palanee and Rees (2014) explored women's experiences of participating in a South African microbicide trial and their experiences of intimate partner violence and conflict.

The HIV prevention responsibilities of South African HVT researchers have been explored (Essack, Slack, et al., 2010), including regarding perspectives on standard of prevention norms in selected ethics guidelines (Moorhouse et al., 2014). The standard of prevention raises several complex ethical and scientific challenges. Standard of prevention norms in ethics guidelines have been debated (cf. Essack, Slack, et al., 2010; Haire et al., 2013; Philpott et al., 2011), decisions on adding new tools to the prevention package have not been easy (Essack, Slack, et al., 2010; Lie et al., 2006) and the prevention packages offered in trials have been variable (e.g., Ngongo, Priddy, et al., 2012). Complexities with standards of prevention in HVTs are the focus of Chapter 5 of this thesis.

Access to care and treatment for participants who seroconvert in trials has been complex and divisive. In South Africa, challenges with access to ART during former President Thabo Mbeki's tenure, further complicated access to treatment. This ethical concern has been vigorously debated (Slack et al., 2005; Stobie & Slack, 2010; Tucker & Slack, 2003) and empirically explored (Barsdorf, Maman, Kass & Slack, 2010), including regarding referral uptake of care services (Clouse et al., 2010) and community perspectives on appropriate benefits (Zvonareva et al., 2013). Given the debate about the responsibilities of sponsors/investigators to address the medical health needs of trial participants, an empirical study on ancillary care practices and perspectives in South African HVTs was undertaken (Slack, 2014).

Concerns that payment of trial participants may compromise voluntariness have been raised by South African HVT stakeholders (Essack, Koen, et al., 2010). While payment to participants should not be considered to offset risk (Wassenaar & Mamotte, 2012),

commentators have argued that it is ethical to compensate research participants for their time and inconvenience (Koen, Slack, Barsdorf & Essack, 2008).

Independent ethics review is both ethically (Emanuel et al., 2004) and legally (NHA, 2003) required. Empirical research has been conducted to identify the resource and capacity building requirements of African RECs for the review of HVT protocols (Milford, Wassenaar & Slack, 2006), and to compare US IRB and South African REC perspectives on the process and content of the ethics review of HVT protocols (Klitzman, 2008). US federal regulations and South African research ethics guidelines have been compared (Cleaton-Jones & Wassenaar, 2010) and the composition, operation and training needs of South African health RECs surveyed in relation to national and international guidelines (Moodley & Myer, 2007).

Informed consent, derived from the ethical principle of respect for autonomy (NCPHSBBR, 1979), is considered a cornerstone of ethical research. The quality of informed consent has been the root of much contention (Emanuel et al., 2004). Issues of informed consent have been considered in the South African context, including the need for cultural sensitivity in the informed consent process, challenges with understanding and comprehension (Lindegger & Richter, 2000), determining the most appropriate methods to assess understanding (Lindegger et al., 2006), exploring perceptions of voluntariness (Wassenaar & Barsdorf, 2005), and investigating communication in the informed consent process (Watermeyer & Penn, 2008). Ethics guideline recommendations on informed consent in trials were rated favourably amongst a sample of South African HVT stakeholders (Moorhouse et al., 2014). South African HVT stakeholders also identified informed consent as a critical ethical concern, particularly given limited access to education and South Africa's socio-political history (Essack, Koen, et al., 2010).

The principle of ongoing respect for participants and communities requires that confidentiality should be protected, participants should be allowed to withdraw from the study without penalty, issues such as research-related injury should be considered, and study results should be communicated to participants (Emanuel et al., 2004). Given negative trial outcomes of some HIV prevention trials, e.g., Cellulose Sulphate and STEP/Phambili, studies have explored perspectives on trial closures (Delany-Moretlwe et al., 2011; Essack et al., 2012) and compensation for research-related injury in cases of harm (Mamotte, Wassenaar & Singh, 2013; Slack, Singh, Strode & Essack, 2012).

6. Summary

This chapter aimed to describe the context of HVTs in South Africa. It outlined the clinical trial process and reviewed selected HIV prevention interventions. The South African HVT landscape was described and the history of the healthcare system, including South Africa's current HIV prevention response, briefly reviewed. The chapter concluded by documenting the literature on ethical issues in South African HIV prevention research, especially HVTs.

Part two of this thesis (Chapters 3-5) reviews the normative and theoretical issues regarding standards of prevention. The following Chapter documents standard of prevention norms in three sets of ethics guidelines and offers a critical review of these.

CHAPTER 3

REVIEW OF STANDARD OF PREVENTION NORMS IN ETHICS GUIDELINES

This chapter reviews ethics guidelines applicable to HVTs (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) to identify standard of prevention norms and to critically evaluate and compare ethics guidance on the standard of prevention. The norms documented in this chapter will serve as a basis for comparison with actual practices reported in the empirical component of this study (see Chapters 7-11).

1. Ethics guidelines specific to HVTs

General ethics guidelines on biomedical research and practice (e.g. CIOMS, 2002; Helsinki, 2013; Nuffield Council on Bioethics, 2002) provide little specific guidance relevant to HIV prevention trials because they were largely developed to address issues relevant to new medical treatments for those who are already ill (McGrory et al., 2010).

As a result, two international ethics guidance documents were developed to deal specifically with biomedical HIV prevention trials, namely, UNAIDS/WHO (2012) *Ethical considerations in biomedical HIV prevention trials* and the companion document UNAIDS/AVAC (2011) *Good participatory practice (GPP) guidelines for biomedical HIV prevention trials*. UNAIDS/WHO (2012) is a revision of UNAIDS (2000) ethics guidance. It was originally published in 2007, but an additional guidance point on IDUs was added in 2012. UNAIDS (2000) was the culmination of several international consultations with various research stakeholders on the ethical issues in HIV prevention research (UNAIDS, 2000). The resulting ethics guidance document on HVTs consisted of 18 guidance points, including one on risk-reduction interventions. These guidelines were revised due to evolution of the HIV prevention field. The revised guidelines (UNAIDS/WHO, 2012) consist of 20 guidance points, including a guidance point on the standard of prevention. Recommendations in these guidelines have been extensively considered in relation to the standard of prevention (e.g., Essack, Slack, et al., 2010; Macklin, 2008; 2009; 2010; 2012; Haire et al., 2012; Haire et al., 2013; Philpott et al., 2011; Rennie & Sugarman, 2010) and have also been assessed by HVT stakeholders (Moorhouse et al., 2014).

The GPP guidelines (UNAIDS/AVAC, 2011) for biomedical HIV prevention trials are a revision of the GPP guidelines (UNAIDS/AVAC, 2007) which emanated from consultations with various research stakeholders that aimed to elucidate the elements of effective partnerships for HIV prevention trials. These guidelines seek to offer mechanisms for systematising community engagement with the aim of providing trial funders, sponsors, and implementers with systematic guidance on how to effectively engage with stakeholders in the design and conduct of biomedical HIV prevention trials (UNAIDS/AVAC, 2011, p. 5). Since their initial publication these guidelines have been widely discussed, promoted and endorsed (Allman, Ditmore & Kaplan, 2014, p. 2), applied to ethical issues in HIV prevention trials (e.g., Koen et al., 2013), implemented in biomedical HIV prevention trials (e.g., Mack et al., 2013), advocated for making decisions on standards of prevention (e.g., Haire et al., 2013), and noted in the U.S. Presidential Commission for the Study of Bioethical Issues (2011), amongst others (see Allman et al., 2014).

There is also South African national ethics guidance applicable to HVTs, namely, MRC (2003) *Guidelines on ethics for medical research: HIV preventive vaccine research*. These guidelines were adapted from the first edition of the UNAIDS guidelines (UNAIDS, 2000) to suit the local South African context given that the UNAIDS document lacked local specificity (MacQueen, Abdool Karim & Sugarman, 2003). These guidelines comprise 18 guidance points, including one on risk-reduction interventions. The South African guidelines (MRC, 2003) are endorsed in South Africa's good clinical practice (GCP) guidelines (DoH, 2006). The National Health Act (2003) legally enforces trial implementers to comply with GCP guidelines (2006) and by inference compliance with MRC (2003) ethics guidelines may be legally mandated. Standard of prevention practices at South African HVT sites are likely to be influenced by South African and international ethics guidelines that are directly applicable to HVTs. Therefore, the sample of ethics guidance documents for review here was limited to the South African ethics guidelines (MRC, 2003) and the two UNAIDS ethics guidance documents (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

There are also other HVT-specific ethics guidance documents, e.g., the *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines* (Kenyan Ministry of Health, 2005) and the *Uganda Guidelines for AIDS Vaccine Research* (Uganda AIDS Commission, 2006). The HIV Prevention Trials Network (HPTN) *Ethics Guidance for Research* was revised by the HPTN in 2009 specifically for an HPTN audience with the aim

to facilitate HPTN's mission by raising awareness of the associated ethical considerations, engaging network members at all levels in discussion about those considerations, and facilitating the integration of ethical considerations into the design and implementation of HPTN research (HPTN, 2009, p. 6). HPTN is a clinical trial network that develops and tests the safety and efficacy of non-vaccine HIV preventative interventions.

2. Desk review of ethics guidelines applicable to HVTs

A desk review was conducted of the three HVT-specific ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) to identify ethical provisions on standards of prevention, and to critically evaluate and compare guidance with regard to standards of prevention.

These HVT-specific guidelines were reviewed for any text dealing with HIV prevention. This text was then extracted verbatim into an MS Word document and clustered according to key dimensions using an inductive-deductive approach (Fereday & Muir-Cochrane, 2006). Text was initially clustered according to five pre-determined dimensions, namely, who should receive prevention methods, what prevention methods should be ensured, why prevention methods should be offered, how decisions should be made, and how access to prevention methods should be ensured. Where necessary, sub-dimensions were developed to better accommodate the text. The remaining text was then clustered according to emerging dimensions (see Appendix 1 for the detailed tabulated coding).

The review of ethics guidelines will hopefully help identify recommendations for guideline developers and will be used to compare ethics recommendations with actual practices in HVTs. To ensure reliability of coding, a second expert researcher in HIV prevention ethics coded a sample of ethical standards in guidance documents. Discrepancies were discussed until consensus was reached.

3. Ethics guideline recommendations for standards of prevention in HVTs

3.1 Why should prevention methods be provided? The ethical rationale

Neither the MRC (2003) nor GPP (UNAIDS/AVAC, 2011) guidelines explicitly refer to any of the four ethical principles of beneficence, non-maleficence, justice or respect for autonomy (NCPHSBBR, 1979) when presenting a rationale for providing prevention methods to trial

participants. According to MRC guidelines (2003, p. 28) “reducing the risk of HIV infection among participants is an essential ethical component of HIV preventive vaccine trials. This is especially critical given that phase III efficacy trials rest on some exposure to HIV infection.” GPP guidelines (UNAIDS/AVAC, 2011, p. 49) specify, “helping trial participants reduce their risk of acquiring HIV is a key ethical obligation of research teams.”

UNAIDS/WHO (2012) identifies beneficence and non-maleficence as the rationales for providing HIV prevention methods to participants. These principles require that potential benefits to participants be maximised and that potential risks be reduced to a minimum. Since HIV infection is the measured endpoint in HIV prevention trials (Lagakos & Gable, 2008), helping enrolled participants remain HIV-uninfected by ensuring access to prevention interventions is in line with the principles of beneficence and non-maleficence. However, there is little consensus amongst ethicists on the ethical rationale for ensuring access to standards of prevention (see Chapter 5). Furthermore, not all ethicists agree that beneficence mandates access to all state-of-the-art prevention methods (Philpott et al., 2011), with some arguing that beneficence places certain limits on obligations (see Chapter 5).

3.2 Who should receive HIV prevention methods? Prevention services for non-trial participants

3.2.1 Recommendations for trial volunteers who screen out

Some trial volunteers will be screened for trials but found ineligible (Ngongo, Priddy, et al., 2012) against the trial’s eligibility criteria (screen-outs). MRC (2003) has a statement (not specific to prevention) that where relevant, protocols should specify referral processes for screen-outs. UNAIDS/WHO (2012, p. 43) guidelines state that “there should be an ongoing iterative consultative process to facilitate local or national decision-making about the appropriate level of support, care, and treatment provided to potential and enrolled participants.” In the guidance point on the standard of prevention, UNAIDS/WHO (2012, p. 46) recommends, “ways should be explored with local authorities to provide trial volunteers and participants with information about HIV prevention and treatment services available in the community.” UNAIDS/AVAC (2011) has no statement on the HIV prevention methods that should be made available to those who screen out of the trial.

3.2.2 Recommendations for the partners of trial participants

MRC (2003) guidelines state that trial participants should be provided with information on how to obtain STI treatment for their partners. UNAIDS/WHO (2012) guidelines do not specify what, if anything, should be provided to the partners of participants. GPP guidelines (UNAIDS/AVAC, 2011) require that in discussions and negotiations on the HIV prevention package, research teams and relevant stakeholders should consider which HIV prevention services will be ensured for participants' partners. However, neither MRC (2003) nor GPP (UNAIDS/AVAC, 2011) guidelines specify how access to potential HIV prevention services should be ensured for partners, that is, provided on-site or through referrals to local healthcare facilities.

3.2.3 Recommendations for host communities

For host communities, MRC (2003) states in the guidance point on care and treatment, that the capacity of the healthcare system should be developed in order to improve the delivery of services to the host community (MRC, 2003). UNAIDS/WHO (2012) specifies in the guidance point on care and treatment, that the health conditions of the community and even the host country should be improved by integrating clinical trials into national plans: 'clinical trials should be integrated into national prevention, treatment, and care plans so that services provided through clinical trials or arrangements brokered for trial participants serve to improve the health conditions of both the trial participants and the community from which they are drawn, and (to) support and to strengthen a country's comprehensive response to the epidemic' (pp. 49-50). GPP guidelines (UNAIDS/AVAC, 2011) have no statement on HIV prevention services for the host community.

The above review suggests that there is little consistency between ethics guidelines on access to prevention services for non-trial participants. In addition, the available guidance is vague regarding exactly which HIV prevention interventions should be ensured for these groups, if any. Only MRC (2003) specifies a mechanism for ensuring access to prevention services for screen-outs and this is limited to referral. However, statements in both MRC (2003) and UNAIDS/WHO (2012) imply that screen-outs should get the standard of prevention that is available in the local healthcare system.

Apart from the statement in GPP guidelines (UNAIDS/AVAC, 2011), there is little direction provided in ethics guidelines on exactly what is owed to partners of participants, their

families, the host community and the host country. Most often, guidelines require that HIV prevention responsibilities to non-trial participants are satisfied by developing the capacity of the healthcare system for the benefit of host communities, which will include partners and families. Given the general silence in guidelines on what is owed to non-trial participants, it has been recommended that such decisions be made in consultation with local stakeholders (Tarantola et al., 2007).

3.3 What should be provided to trial participants? The substantive ethical standard

South African guidance asserts that the “most appropriate risk-reduction counselling and access to preventive methods should be provided to all trial participants” (MRC, 2003, p. 28). UNAIDS/WHO (2012, p.45) requires that “researchers, research staff, and trial sponsors should ensure that appropriate counselling and access to all state of the art HIV risk-reduction methods are provided to participants.” GPP guidelines (UNAIDS/AVAC, 2011, p. 48) do not outline a substantive position but do define the standard of prevention as “the package of comprehensive counselling and state of the art HIV risk reduction methods provided or made available to participants in biomedical HIV prevention trials.”

Ethics guidelines advocate for access to *optimal* (MRC, 2003) or *state-of-the-art* (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) prevention methods. MRC (2003) and UNAIDS/WHO (2012) guidelines contend that *access* to prevention methods should be ensured for trial participants and that “appropriate” risk-reduction counselling is *provided*. The obligation to provide “access” is weaker than the obligation to actually provide prevention interventions (Lie et al., 2006) – “actual provision” entails that researchers themselves should “actively provide” the intervention (Lie et al., 2006) whereas “access” entails either direct on-site provision of services or referral (Philpott et al., 2011; UNAIDS/AVAC, 2011) through established partnerships, and ensuring that no barriers (economic or other) impede uptake by participants (Lie et al., 2006). Further, guidelines (MRC, 2003; UNAIDS/WHO, 2012) do not indicate what is meant by “appropriate” risk-reduction counselling. This term may be interpreted, and thus implemented, differently by different stakeholders.

Guidelines (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) do not define “state-of-the-art”. This critical concept is left open to interpretation. It is possible that the state-of-the-art will differ by locale. However, given that UNAIDS/WHO (2012) guidelines aim to minimise

double standards between developed and developing countries (Haire et al., 2013), it is likely that state-of-the-art is not intended as context-dependent but defined according to the best available standard anywhere in the world.

All ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) address the issue of the standard of prevention that should be provided to trial participants in HVTs. Given the more recent introduction of the term “standard of prevention” (cf. Macklin, 2008), issues of HIV prevention are dealt with under risk-reduction interventions in the MRC (2003) guidelines.

3.4 What should be provided to trial participants? The components of the package

Guidelines specify that the following HIV prevention interventions should be included in the standard of prevention package:

- Comprehensive risk-reduction counselling (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), including partner and couples counselling (UNAIDS/AVAC, 2011). Comprehensive counselling should include basic principles of safer sexual practices and safer injecting practices; education concerning general health and treatment of STIs; reproductive health; and strategies to reduce domestic violence (UNAIDS/WHO, 2012)
- Access to male and female condoms (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), with appropriate instructions and demonstrations (UNAIDS/AVAC, 2011)
- Testing for (UNAIDS/AVAC, 2011) and treatment of STIs (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012)
- VMMC, where applicable (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012)
- Counselling about the potential benefits and risks of PEP and how it can be accessed (MRC, 2003; UNAIDS/WHO, 2012)
- Access to PEP (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012)
- Sterile injecting equipment and medical substitution therapy for IDUs (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012)
- State-of-the-art reproductive healthcare services (UNAIDS/WHO, 2012)

There is some consistency across guidelines regarding the prevention components that should be included in the package. While the above components are listed in the commentary section of various guidance points, it is also required that this package will be enhanced as new prevention methods are found effective (see 4. below).

Components identified in MRC (2003) are somewhat outdated given evolutions in HIV prevention. However, the statement that “preventive methods should include, but not necessarily be limited to” the list of specified interventions, suggests that MRC (2003, p. 29) sets a minimum standard of prevention that could be ratcheted up. This is in contrast to UNAIDS/WHO (2012) which establishes a ceiling (state-of-the-art) to be negotiated down. Further, recommendations that new methods should be added to the package as they are discovered and validated (MRC, 2003) indicate latitude to include prevention methods that are not on the list of identified components.

While MRC (2003) states that investigators are morally compelled to provide optimal risk-reduction methods, this guidance document does not require the actual provision of PEP. Since PEP is only accessible in limited circumstances (occupational exposures and sexual assault) in the South African context, this may suggest that these guidelines benchmark optimal in relation to national rather than international standards.

UNAIDS/WHO (2012) also identifies components related to reproductive healthcare under the standard of prevention. However, the standard of prevention seems like an inappropriate category for these ancillary care services. GPP guidelines (more appropriately, it could be argued) contend that sexual and reproductive healthcare are examples of non HIV-related care, and “not directly related to HIV prevention” (UNAIDS/AVAC, 2011, p. 55).

3.4.1 Specific requirements for risk-reduction counselling

MRC (2003) and UNAIDS/WHO (2012) guidelines specify several requirements for risk-reduction counselling, including that counselling should be based on reliable information about the prevailing social and behavioural characteristics of the research population. However, there is some concern that relying on research staff to provide risk-reduction counselling and HIV prevention interventions to participants while conducting a trial that uses HIV infection as an endpoint introduces a conflict of interest or “researchers’ dilemma” (de Zoysa et al., 1998; Slack et al., 2000). For this reason, guidelines (MRC, 2003;

UNAIDS/WHO, 2012) recommend that consideration be given to providing counselling and other risk-reduction interventions through an independent agency. However, it has been argued that this may in fact compromise rather than strengthen researchers' abilities to meet ethical obligations to trial participants (Chatterjee, de Zoysa, Farley, Hankins & Mane, 2006, p. 2). Further, empirical studies of care and prevention in microbicide trials concluded that concerns that research staff would compromise risk-reduction efforts in order to facilitate research, were unfounded (Heise et al., 2008).

MRC (2003) also requires that counselling should be conducted in accordance with national guidance, and should be appropriate to the participant's language, age and gender.

UNAIDS/WHO (2012, p. 47) requires that the community-government-investigator-sponsor partnership should agree on the technique, frequency and message content of counselling sessions.

GPP guidelines (UNAIDS/AVAC, 2011) suggests that risk-reduction counselling should include both partner and couples counselling and that local and community stakeholders make inputs into counselling approaches during protocol development.

3.5 How decisions should be made on what to provide? The current package

Various factors to be considered in decision-making about the standard of prevention are identified in guidelines including stakeholder consultation, input from RECs, post-trial continuity and support, and government and sponsor policies, as detailed below.

3.5.1 Stakeholder consultation

All guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) endorse consultation with stakeholders, including the community, on the HIV prevention methods to be provided to participants in HIV prevention trials. These include consultations on:

- The design of an effective risk-reduction strategy (MRC, 2003; UNAIDS/WHO, 2012)
- Determining the components of the HIV prevention package (UNAIDS/AVAC, 2011)
- Input into appropriate risk-reduction interventions (MRC, 2003)

- The method and process for monitoring risk-reduction interventions (MRC, 2003; UNAIDS/WHO, 2012)
- Implementation and monitoring of risk-reduction interventions, including uptake and standards of referral services (UNAIDS/AVAC, 2011)
- Tailoring the design, implementation, and oversight of risk-reduction interventions (UNAIDS/WHO, 2012), and
- Establishing the type, scope, and process by which participants are provided with, or referred to, services to access the full HIV prevention package (UNAIDS/AVAC, 2011).

MRC (2003) identifies a role for stakeholder consultation in decision-making before (designing interventions) and during (monitoring interventions) the research process, with stakeholders having a role in determining -what prevention methods should be provided to participants as well as -how to monitor them.

UNAIDS/WHO (2012, p. 13) identifies a role for stakeholder consultation in terms of designing, implementing and monitoring risk-reduction interventions. In addition, these guidelines state that -prevention trials should not be conducted when agreements have not been reached among all research stakeholders on ... the standard of prevention. Therefore, stakeholders have a role in determining -what prevention methods to provide and -how to implement them.

UNAIDS/AVAC (2011) also identifies a role for consultation in determining -what prevention methods are provided and -how to implement them.

Consultation regarding mechanisms for implementation of prevention methods is ethically uncontroversial. However, the procedural requirement for consultation on the standard of prevention package is incongruous given the substantive standard is that trial participants should be provided with access to all state-of-the-art (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) prevention methods. Such consultation may inadvertently lower the substantive standard when the ethical goal is to determine -what should be provided to participants (Essack, Slack, et al., 2010; Haire et al., 2012). There is no guidance on how the substantive and procedural standards must work together or how to resolve any tensions

between these standards. Furthermore, given that stakeholders may have vastly different perspectives, there may be instances where agreement cannot be reached on what standard of prevention to provide participants. In such cases, UNAIDS/WHO (2012) guidelines recommend that trials should not be conducted. This very rigid recommendation may impede the discovery of effective and needed prevention interventions. In addition, guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) require consultation with various stakeholders on the standard of prevention but none provide any ethical rationale for consulting stakeholders on this issue. It seems plausible that this requirement is based on the principle of respect for communities, which confers on the researcher an obligation to respect the values and interests of the community in research and, wherever possible, to protect the community from harm (Weijer, Goldsand & Emanuel, 1999, p. 275).

A further criticism is that certain guidelines (MRC, 2003; UNAIDS/WHO, 2012) only specify the outcomes of consultation. They provide little direction on how to operationalise stakeholder consultations, including which stakeholder groups should be included or the content of such consultations. While guidelines require that some decisions should be made via discussions (UNAIDS/AVAC, 2011) and negotiations (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), there is little direction on what format the consultations should take (e.g., large stakeholder meetings). There is also a paucity of information on the feasibility of stakeholder consultations before every trial, given the requisite time commitments and cost implications.

A gap in both the MRC (2003) and UNAIDS/WHO (2012) guidelines is that relevant stakeholders are not always identified or when stakeholders are specified, they seldom include all research stakeholders. Further, involving all research stakeholders in decision-making has not been common practice to date (McGrory et al., 2010). There is also concern that in multi-centre trials, consultations may actually lead to different recommendations and expectations about the type of prevention package that should be provided (McGrory et al., 2010, p. 30) at each site, creating potential differences in outcomes for participants. Of course vague guidelines permit trial implementers some flexibility and it is often a virtue to leave a guideline intentionally somewhat vague, in order to enable decision makers to make different determinations depending on the circumstances. That is a better strategy than having to make exceptions to rules that are too rigidly defined in advance (Macklin, 2012, p. 32). Nevertheless, vagueness may create challenges for implementation.

Despite these criticisms, stakeholder consultation may be valuable for making decisions about how to implement the established substantive standard, for example, by making inputs into whether local providers are capacitated to provide risk-reduction services and understanding the cultural nuances that may affect participant uptake of prevention services (cf. Mark et al., 2012).

3.5.2 *REC input*

MRC (2003) guidelines specify a role for RECs in approving both the risk-reduction strategy and plans for monitoring risk-reduction interventions.

According to UNAIDS/WHO (2012, p. 57) “the appropriateness of plans to monitor risk-reduction interventions should be determined by the scientific and ethical review committees that are responsible for providing prior and continuing review of the trial.” However, UNAIDS/WHO (2012) does not explicitly require that RECs approve the risk-reduction package and these guidelines omit the “standard of prevention” in the list of items for scientific and ethical review. However, given recommendations to review informed consent procedures and information sheets which are required to include information on risk-reduction interventions, it could be argued that RECs should review standard of prevention packages. Generally, it is accepted that ethics review of HVT protocols considers the standard of prevention to be provided to participants (Tarantola et al., 2007).

UNAIDS/AVAC (2011) has no explicit requirement that RECs actually review and approve the risk-reduction package.

3.5.3 *Post-trial access to prevention methods*

There are general statements in MRC (2003) and UNAIDS/WHO (2012) stating that access to services, specifically counselling, should be available post-trial, for example, participants should be provided with “supportive counselling for the duration of the trial, and appropriate referral after the trial is completed” (UNAIDS/WHO, 2012, p. 18).

3.5.4 *Government and sponsor policies*

All guidelines consider governments and sponsors as key research stakeholders to be involved in consultations on the standard of prevention. However, only UNAIDS/AVAC (2011) acknowledges that national-legal restrictions and funding-body restrictions may

influence the prevention package provided to participants. Where funding restrictions limit which prevention methods can be covered by the study budget, the onus is on the research team to find alternative ways to ensure access to these prevention methods (UNAIDS/AVAC, 2011).

3.5.5 Trial design and population

GPP (UNAIDS/AVAC, 2011) is the only guideline that requires consideration of the “appropriateness for the trial design and population” (UNAIDS/AVAC, 2011, p. 50) when making determinations about the prevention package. So, for example, the provision of sterile injecting equipment should be considered in relation to whether the trial population includes IDUs or not.

4. How should decisions be made on adding new methods to the prevention package?

From the guidelines, three criteria should be used to make decisions on adding new methods to the prevention package, namely, scientific validity, regulatory approval and stakeholder consultation.

MRC (2003, p. 29) suggests that adding new methods should be determined by considering scientific evidence: “As new methods of prevention are discovered and validated, these must be added to the preventive methods offered to trial participants.” There is no role identified for regulatory approval and stakeholder consultation in making decisions on the enhancement of the prevention package.

UNAIDS/WHO (2012, p. 45) recommends consideration of scientific validity, normative approval and stakeholder consultation when making decisions on adding new prevention methods: “new methods should be added, based on consultation among all research stakeholders, as they are scientifically validated or approved by relevant authorities.”

GPP (UNAIDS/AVAC, 2011, p. 49) states that “research teams may need to review the HIV prevention package regularly, taking into consideration new HIV counselling models and risk reduction methods that are scientifically validated and, when appropriate, approved by national bodies for use.”

Requirements across UNAIDS companion guidelines (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) are inconsistent: approval is recommended as an *alternative* to scientific validation (UNAIDS/WHO, 2012) as opposed to *in addition to* scientific validation (UNAIDS/AVAC, 2011). Further, while UNAIDS/WHO (2012) recommends approval by relevant authorities, UNAIDS/AVAC (2011) recommends approval by national bodies. Such inconsistencies may create implementation challenges for HVTs.

Further, none of the ethics guidelines address what criteria constitute “scientifically validated” or “approved by relevant authorities”. While enabling flexibility in decision-making, such vagueness may create practical challenges for implementation.

UNAIDS/WHO (2012, p. 47) specifies that when making decisions on an evolving standard of prevention, negotiations should consider the following scientific criteria: “feasibility, expected impact and the ability to isolate the efficacy of the biomedical HIV modality being tested”. It has been argued that this latter procedural requirement (i.e., negotiation) is the solution to concerns that providing participants with all state-of-the-art prevention methods is infeasible and impractical (cf. Macklin, 2009). Given that these are the only specified considerations for consultation, it is unclear whether resource constraints or cultural and religious objections to the provision of prevention methods would be considered legitimate objections to a state-of-the-art package in terms of feasibility. It is also unclear why all research stakeholders should be consulted on such decisions, when only a few stakeholder groups, like scientists and statisticians, may possess the requisite skills to make such feasibility determinations (cf. Haire et al., 2013). Further, stakeholders may object to the addition of prevention methods like VMMC for religious or cultural reasons. If VMMC is not provided, then consultation would have lowered the substantive standard of ensuring access to all state-of-the-art prevention intervention (UNAIDS/WHO, 2012), and would arguably compromise the welfare of individual research participants. If VMMC is provided despite these objections, then stakeholder consultation is tokenistic and does not appropriately satisfy the principle of respect for communities. This illustrates the tension between having established substantive standards in conjunction with procedural requirements for consultation on substantive standards. It also highlights the tension between protecting individual research participants as espoused in most research ethics frameworks, versus the promotion of societal or community health goals advocated in public health frameworks (Buchanan & Miller, 2006).

5. What should be in the protocol?

The research protocol should:

- Specify referral processes for those persons excluded from the trial (MRC, 2003)
- Outline potential risks, and steps that will be taken to reduce these risks to a minimum. Risk minimisation measures include providing participants with risk-reduction interventions (MRC, 2003; UNAIDS/WHO, 2012)
- Set out mechanisms for negotiation among all research stakeholders, including the community, about the standards for enhancement of the risk-reduction package (UNAIDS/WHO, 2012), and
- The prevention standard should be defined in the study protocol (UNAIDS/WHO, 2012).

UNAIDS/AVAC (2011) has no statement on what should be included in the protocol.

Study protocols are blueprints of research and provide detailed descriptions of the plan for conducting the HVT, including the purpose of the study and ethical considerations. Protocols are also submitted for ethical and scientific review and therefore should be comprehensive enough so that review bodies can make valid determinations. As a particularly complex and contentious ethical issue (cf. Macklin, 2008), it is critical that the standard of prevention is included in the study protocol.

6. What should be in the informed consent form and process?

MRC guidelines (2003, p. 18) state that "participants must be informed of and should understand the risks and risk minimisation measures that will be taken, and these measures should be included in the informed consent form." However, including the standard of prevention in the informed consent form (ICF) does not absolve trialists of the responsibility to counsel participants on the risk-reduction efforts that are available. To this end, the guidance point on informed consent specifies that "each prospective participant must be counselled, using appropriate language and techniques, to understand ...that they will receive counselling and access to the means of risk-reduction..." (MRC, 2003, p. 22).

UNAIDS/WHO (2012, p. 45) states that "if the study aims to test a product by comparing its additive effects to those of routinely practiced prevention, in all cases this prevention

standard should be defined in the study protocol as well as in informed consent documents.ö Similarly to MRC (2003) guidelines, ðeach prospective participant must be informed... that they will receive counselling concerning how to reduce their risk of HIV exposure and access to risk-reduction means (in particular, male and female condoms, clean injecting equipment, and where relevant, male circumcision)...ö (p. 54).

While UNAIDS/AVAC (2011) is silent on whether details on the standard of prevention should be included in the consent form or process, MRC (2003) and UNAIDS/WHO (2012) contain very clear guidance that the prevention measures that will be provided to participants should be outlined in both the ICF and the informed consent process.

7. How should access to prevention methods be ensured?

Various mechanisms are identified in guidelines regarding ensuring access to prevention methods, namely, research, capacity building, partnership, referral, and advocacy, as detailed below.

7.1 Formative research on HIV prevention interventions available in the trial community

MRC (2003) requires that risk-reduction ðcounselling should be...based on reliable information about the prevailing social and behavioural characteristics of the research populationö (p. 29). However, these guidelines do not recommend that formative research should be conducted to ensure that prevention methods are acceptable to, and can be accessed by participants during the trial.

While there is no recommendation to conduct formative research on the services currently available in the local community, UNAIDS/WHO (2012, p. 49, italics added) requires that ðtrial sponsors and researchers should collaborate with governments in low- and middle-income countries to *explore*, develop, and strengthen national and local capacity to deliver the highest possible level of HIV prevention, care, and treatment services.ö

UNAIDS/AVAC (2011, p. 50) states that ðresearch teams determine which stakeholders already provide HIV prevention interventions, what types of services they provide, and their capacity to provide adequate services.ö Such formative research is important in mapping the existing prevention services available in the community, areas where the capacity of local

providers needs to be developed, and will enable research teams to provide optimal referrals and make linkages when necessary (UNAIDS/AVAC, 2011, p. 50).

7.2 Capacity building

Ethics recommendations pertaining to capacity building in MRC (2003) guidelines focus mostly on risk-reduction counselling and specifically require that the capacity of community members to be counsellors should be developed and that risk-reduction counsellors should receive adequate training, supervision and support. There is also a general statement in the guidance point on care and treatment that sponsors and investigators should build capacity of trial linked healthcare centres to deliver services to the host community (MRC, 2003, p. 31) and that the capacity of trial-linked healthcare service centres in the host community should be strengthened (p. 33). These guidelines do not prescribe how such capacity should be developed. Therefore, capacity building may include a range of strategies from information sharing to the provision of resources.

UNAIDS/WHO (2012) guidelines make recommendation to build capacity to deliver prevention methods by training counsellors to provide culturally acceptable and sustainable risk-reduction counselling. In addition, researchers should guarantee that all communities engaged in biomedical HIV prevention trials have state of the art reproductive healthcare services (UNAIDS/WHO, 2012, p. 45). These guidelines also recommend that local and national capacity should be developed to improve health conditions of both trial participants and host communities by integrating clinical trials into national prevention plans (UNAIDS/WHO, 2012). Further, trial sponsors and researchers should collaborate with governments in low- and middle-income countries to explore, develop, and strengthen national and local capacity to deliver the highest possible level of HIV prevention, care and treatment services through strategic investment and development of trial-related resources (UNAIDS/WHO, 2012, p. 49). These guidelines prescribe that capacity development should include strategic investment and development of trial-related resources.

In terms of the standard of prevention, UNAIDS/AVAC (2011) limits capacity building to stakeholder education efforts about HIV, HIV prevention options and general research literacy.

While both MRC (2003) and UNAIDS/WHO (2012) contain specific capacity building requirements to facilitate and/or enhance the delivery of prevention services to trial participants, UNAIDS/WHO (2012) also addresses capacity building efforts to improve access to services for the host community and even for the host country.

7.3 Partnership

MRC (2003) is silent on establishing partnerships with other stakeholders in order to ensure access to prevention methods for trial participants.

UNAIDS/WHO (2012) identifies partnership mechanisms to ensure provision of prevention services. However, these recommendations are located in different guidance points across the document. These guidelines recommend collaborating with governments to explore, develop, and strengthen national and local capacity to deliver the highest possible level of HIV prevention. They recommend collaborating with local authorities to explore ways to provide trial volunteers and participants with information about the HIV prevention interventions available in the community. In addition, they recommend that the responsibility to ensure access to prevention services is shared, and located primarily with the local health system.

UNAIDS/AVAC (2011) recommends making linkages with, and consulting local service providers in order to ensure optimal referral networks.

Empirical research studies on care (MacQueen, McLoughlin, Alleman, McClain Burke & Mack, 2008; Slack, 2014) have identified partnerships as a critical strategy in ensuring access to services in HIV prevention trials. Future revisions of MRC (2003) guidelines should consider providing some direction on strategic partnerships in ensuring access to prevention interventions.

7.4 On-site provision and referrals

HIV prevention interventions may be provided to participants directly (on-site) or through referrals (UNAIDS/AVAC, 2011).

MRC (2003) states that referral networks should be established for those who screen out of the trial. For participants, referral networks should be monitored and appropriate referrals should be made post-trial for access to ongoing counselling. However, there is no explicit

recommendation that referral mechanisms should be established for participants during the trial.

UNAIDS/WHO (2012, p. 46) has clear guidance on referrals for trial participants stating that “referral mechanisms should be established and follow-up mechanisms instituted to ensure quality case management services.” These guidelines also specify that trials should only be conducted in communities where participants can be referred to ongoing psychosocial services.

UNAIDS/AVAC (2011, p. 51) recommends that “research teams and relevant stakeholders discuss and negotiate the comprehensive HIV prevention package, taking account....the HIV prevention services and options that will be offered through referral mechanisms.”

Except the recommendation to outsource risk-reduction counselling, none of the guidelines specify which prevention services should be provided on-site and which should be referred. By stating that researchers should ensure access to prevention services (UNAIDS/WHO, 2012), either strategy may be utilised to provide prevention services. However, when prevention interventions are ensured through referrals, it is incumbent on researchers to ensure that participants actually access these services. This lack of specification seems appropriate because the availability of prevention services in local communities is not standard or static. These recommendations suitably allow access strategies to be informed by the local context.

7.5 The role of advocacy in ensuring access to prevention interventions

UNAIDS/WHO (2012) identifies a role for advocacy in ensuring access to prevention services, particularly those considered illegal in some contexts, e.g., provision of clean needles. MRC (2003) states in the guidance point on vulnerability that advocates could play a role in addressing the needs of legally marginalised communities like IDUs, and GPP (UNAIDS/AVAC, 2011) requires consideration of current national laws in making determinations on the prevention package. It has been argued that when it is not legally permissible to provide participants with HIV risk-reduction interventions like clean needles, researchers should consider the appropriateness of conducting HIV prevention trials with IDUs in such contexts (Mamotte, 2012). The closure of PrEP trials in Cambodia and Cameroon provide important evidence of the role of advocacy in trials and the consequences

of failure to provide an optimal prevention package (Singh & Mills, 2005). There are many opportunities to advocate for the provision of better HIV prevention interventions such as the CDC PrEP trial in Thailand among IDUs where participants were provided with counselling, condoms, STI treatment, and follow-up in a methadone drug treatment programme but not with clean needles. Some contend that access was restricted by US government policy that prohibited provision of clean needles (Haire, 2011).

8. What should be monitored?

The monitoring of risk-reduction interventions forms part of an entire guidance point in both MRC (2003) and UNAIDS/WHO (2012) guidelines. MRC (2003) recommends that consideration should be given to employing an independent agency to monitor risk-reduction interventions in order to avoid conflict of interest concerns, while UNAIDS/WHO (2012) recommends that the clinical trial monitor should monitor counselling standards.

GPP guidelines (UNAIDS/AVAC, 2011, p. 51) recommend ensuring the quality of referral mechanisms as well as monitoring the uptake of prevention services during the trial.

All three guidelines require that risk-reduction interventions and referral mechanisms should be monitored, for example, before a trial commences, researchers, trial sponsors, countries, and communities should agree on a plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction intervention, including counselling and access to proven HIV risk-reduction methods (UNAIDS/WHO, 2012, p. 56).

9. What should be documented?

Only GPP guidelines (UNAIDS/AVAC, 2011) require certain aspects of the trial and related discussions to be documented. With regard to standards of prevention, these guidelines specify that research teams maintain clear written records of discussions and agreements. This includes recommendations, actions taken by the research team, and any unresolved issues that require follow-up (p. 51).

Given the emphasis on stakeholder consultation across all the guidelines, the absence of recommendations for documentation of these discussions is a major oversight. Further, since monitoring is a requirement of all guidelines, it is logical that this should also require documentation.

10. Summary

This chapter reviewed ethics recommendations on standards of prevention in three HVT-specific ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). These standard of prevention norms will be used as a basis of comparison for standard of prevention practices identified in the empirical component of this study. In the main, these guidelines are fairly consistent in their HIV prevention requirements. These similarities are to be expected because MRC (2003) is an adaptation of UNAIDS (2000) guidelines ó an earlier version of UNAIDS/WHO (2012) ó and UNAIDS/WHO (2012) and UNAIDS/AVAC (2011) are companion documents. Nevertheless, there are a few (but not insignificant) differences on standard of prevention norms between guidelines.

All guidelines indicate the standard of prevention that should be provided to participants. However, South African guidelines (MRC, 2003) set a minimum standard of prevention that could be ratcheted up while UNAIDS/WHO (2012) guidelines establish a ceiling to be negotiated down.

The ethical rationale for ensuring access to standards of prevention in trials is not consistent across guidelines, and only UNAIDS/WHO (2012) explicitly identifies ethical principles of beneficence and non-maleficence as underpinning obligations to ensure access to all state-of-the-art prevention interventions.

Ethics recommendations for non-enrolled persons (participantsøpartners, families, and host communities) are fairly fragmented. Exactly what standard of prevention is owed to these moral groups, if anything, is not adequately articulated in guidelines.

Guidelines also make recommendations for the enhancement of the prevention package, requiring scientific validation (MRC, 2003; UNAIDS/AVAC, 20112) and/or approval by relevant authorities (UNAIDS/WHO, 2012) or national bodies for use (UNAIDS/AVAC, 2011). This difference between national and the broader òrelevant authoritiesö may be of relevance during implementation. The use of indeterminate concepts may create challenges for implementation ó stakeholders may be unclear about what is required of them, or may interpret these requirements differently, since they are not predefined.

The next chapter reviews some frameworks/criteria for operationalising ethics guideline recommendations of scientific validity and stakeholder consultation.

CHAPTER 4

A REVIEW OF FRAMEWORKS FOR OPERATIONALISING STANDARD OF PREVENTION DECISION-MAKING

There are several models for ethical decision-making in various professions and disciplines including, medical practice and psychology. However, there are very few models for decision-making in research, and even fewer for clinical research.

The available normative framework for decision-making about standards of prevention in HVTs is ethics guidelines. As outlined in Chapter 3, ethics guideline requirements for the standard of prevention include access to ‘optimal’ or ‘state-of-the-art’ HIV risk-reduction interventions. In addition, new tools should be added to the prevention package as they are:

- Discovered and validated (MRC, 2003)
- Scientifically validated *or* approved by relevant authorities (UNAIDS/WHO, 2012)
- Scientifically validated *and* when appropriate approved by national bodies for use (UNAIDS/AVAC, 2011).

Further, UNAIDS/WHO (2012, p. 47) requires a process of stakeholder consultation when adding new tools which considers the ‘feasibility, expected impact, and the ability to isolate the efficacy of the biomedical HIV modality being tested.’ There is some concern that such consultations may result in suboptimal prevention packages and undermine the substantive standard that the package be state-of-the-art (Essack, Slack, et al., 2010; Haire et al., 2012).

As identified in Chapter 3, guidelines propose concepts for determination of the standard of prevention (e.g., state-of-the-art, scientific validation, consultation, negotiation) that are equivocal, and difficult to operationalise. Guidelines do not specify the criteria that constitute ‘scientifically validated’ or ‘approved by relevant authorities’ This is problematic because these conditions are defined differently by different regulatory and normative bodies (Philpott et al., 2011) and can be interpreted as delineating different phases of product development (Jay et al., n.d.).

An unpublished framework (Jay et al., n.d.) arguably the most developed (although not yet piloted to determine its pragmatic value) is reviewed below. It is relevant because of its

potential to facilitate decision-making on the enhancement of the prevention package. A set of ‘consensus’ criteria are also reviewed (McGrory et al., 2010; Philpott et al., 2011). These criteria were developed at an international workshop on standards of prevention, in which the present author participated.

There are available (and contested) procedural approaches for making decisions, e.g., ‘accountability for reasonableness’ (Daniels, 2000, p. 1300). This chapter also reviews a framework that delineates the process (and content) for stakeholder consultation (Tarantola et al., 2007) that appears to be endorsed by guidelines (cf. UNAIDS/WHO, 2012) and by others (cf. Hankins, Osmanov & Gutnick, 2009).

1. The three-step framework for making decisions on the standard of prevention

One of the key complexities with the standard of prevention is how to make decisions on the enhancement of the prevention package. This issue has become especially pertinent as new HIV prevention interventions have been proven effective, including VMMC and more recently, PrEP.

1.1 Aims of the framework

This framework aims to address some of the vagueness, ambiguity and inherent tensions in ethics guidelines (see Chapter 3). It delineates when a new prevention intervention should presumptively be provided to participants and when this obligation may be modified on scientific grounds (Jay et al., n.d.). However, it is not intended as a substitute for processes requiring stakeholder consensus on clinical trial designs (Jay et al., n.d.).

1.2 The three phases

1.2.1 Step 1: Validation for clinical use

The key question driving step one is: has the new prevention intervention been validated for use? The framework clearly articulates when not to, and when to, add new prevention interventions to the prevention package. New prevention interventions *should not* be provided to participants:

- too early: before its effectiveness (benefit) is conclusively established;
- too late: only after it is introduced in the local healthcare system; nor

- in a haphazard manner: without consideration of appropriate combinations.

Instead, new prevention methods *should be* included in the prevention package when the intervention has been validated for clinical use in the context where the trial is being conducted and among the enrolled populations. Several criteria are outlined as relevant to determinations of clinical validation, namely:

- Data on safety and efficacy in comparable populations as well as the strength of data especially when the data from multiple trials conflict;
- The similarity between the study populations and those who will be participating in the planned trial;
- Behavioural considerations which could amplify or decrease the value of the intervention, either alone or in combination with other modalities;
- The acceptability and desirability of the intervention among the populations(s) participating in the planned trial; and
- Considerations of cost and delivery which could influence the real-world applicability and scalability of the prevention intervention.

The concept of clinical validation is helpful in clarifying some of the nebulousness related to guideline (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) recommendations for scientific validation. While it is acknowledged that this approach does not make decision-making easy, the validation requirement clarifies the relevant criteria to consider and the limits to researchers' obligations. Such clarity may be helpful for trial implementers and may also subvert the potential of multiple interpretations, and therefore limit variability in the standard of prevention (when such variability is driven by challenges with interpretation rather than context-specific determinations). Furthermore, it is not required that researchers routinely provide all available prevention interventions without a careful appraisal of benefits to participants nor does it mean that researchers can merely rely on modalities available in the public healthcare system.

The framework describes that validation is not dependent on regulatory approvals. In this way, it may be helpful in clarifying potential challenges identified in Chapter 3 regarding the equivocal and inconsistently applied concept of regulatory approval, including whether any approval or national approval is a prerequisite for the enhancement of the prevention

package. In resource-constrained contexts, it is argued that if the prevention intervention is considered an appropriate, realistic practice but has not been instituted in the local healthcare system only due to cost, the validation threshold is satisfied (Jay et al., n.d.). In these circumstances, research may serve to ratchet up the local system. However, in cases where the provision of the intervention would severely tax the current and foreseeable capacity of the local healthcare system, and is perceived as unsustainable and an inappropriate use of clinical resources, then that prevention intervention is not considered validated. The authors contend that researchers should not introduce long-term prevention modalities knowing that these would not be sustained post-trial (Jay et al., n.d.). However, others have argued that the immediate potential benefit of reduced HIV infection risk for participants is a legitimate trial-related benefit (Haire et al., 2013).

1.2.2 Step 2: Methodological necessity

Step 2 is driven by the question of methodological necessity: is withholding the prevention intervention methodologically necessary to answer the study question(s)? Once the prevention intervention is validated for clinical use (Step 1 above), ethically, it must be provided to trial participants (Jay et al., n.d.). However, the authors specify that prevention interventions “may be withheld when *methodologically necessary* to address a *compelling public health question*” (Jay et al., n.d., p. 11), subject to the agreement of the community.

Methodological necessity is explained as only existing when “it is impossible to answer the study question while providing the most clinically reasonable prevention package to all participants” (Jay et al., n.d., p. 11). This is similar to the feasibility threshold described in guidelines (UNAIDS/WHO, 2012) and highlights the tension between researcher’s scientific and ethical responsibilities in that:

- the study intervention cannot be adequately evaluated in combination with the newly validated modality because their mechanisms of action are too similar;
- the newly validated modality is so effective that showing an added effect from the study intervention will require a sample size and/or duration that is substantially misaligned with a reasonable allocation of resources; or
- the newly validated modality cannot reasonably be procured, due to issues relating to manufacturing or licensure. (When an unlicensed product can be obtained, regulatory status alone does not create methodological necessity for withholding it.)

It is recommended that feasibility determinations should consider alternative trial designs, including the use of active controls (cf. Haire, 2014) designed to demonstrate superiority of the experimental product as compared to the control. This will permit sample sizes comparable to recent efficacy trials.

1.2.3 Step 3: Compelling public health need

The key question driving step three is: does the study address a compelling public health need in the setting where it will take place? While the authors anticipate that the standard of prevention would be resolved at one of the first two steps, in some instances if the provision of a clinically validated prevention intervention is not methodologically possible, the social value of the research is considered. Only in circumstances where research addresses a compelling public health need in the host community, can withholding an otherwise ethically required prevention intervention be justified (Jay et al., n.d.). A compelling public health need is defined as contributing to prevention efforts and offering “the prospect of a true ‘game-changer’ with respect to the local epidemic” (Jay et al., n.d., p. 13). Of course, such judgements may rely on the opinions of experts, which may differ.

In addition, a suboptimal prevention package is only acceptable with thorough consultation and the express agreement of host communities and other local stakeholders such as health officials and local RECs in accordance with processes outlined in GPP guidance (UNAIDS/AVAC, 2011). Figure 4 graphically captures the three decision-making steps when adding new tools to the prevention package.

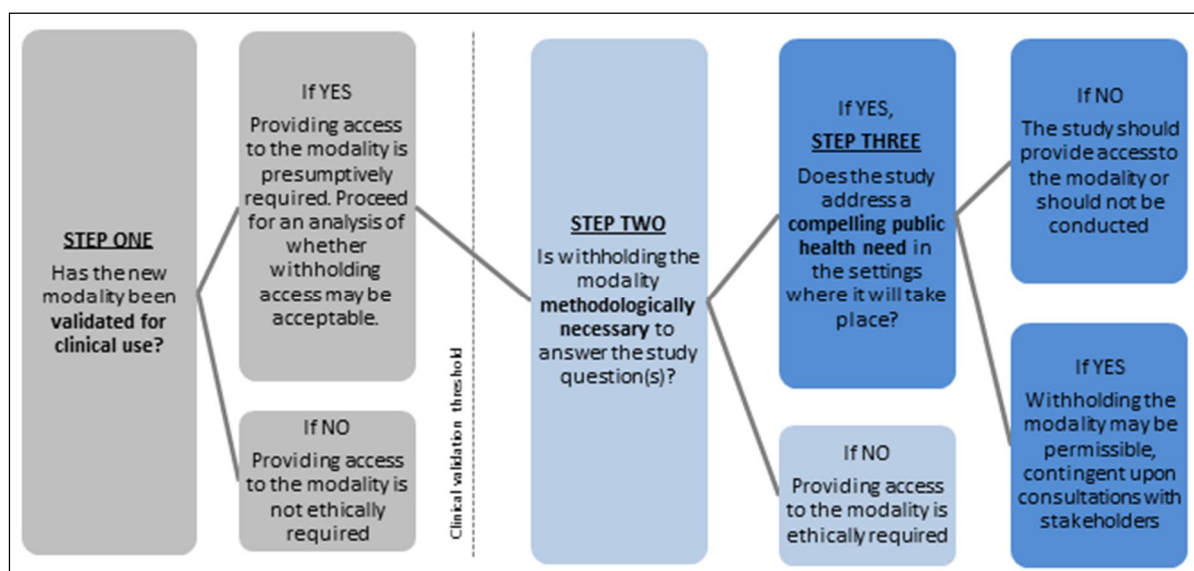


Figure 4: The three-step framework for making decisions on the standard of prevention (Jay et al., n.d.).

This framework provides a promising model for making decisions about when and how to add new tools to the prevention package. It helps clarify requirements in ethics guidelines by delineating requirements for clinical validation and attempting to clarify considerations regarding the feasibility threshold.

2. Criteria for decision-making on standards of prevention

In 2009, a consultation on standards of prevention was held in Uganda to explore challenges with operationalising existing guidelines and develop criteria to help research stakeholders implement guidance (Philpott et al., 2011). Meeting delegates established specific criteria to guide standard of prevention deliberations, as follows:

1. If an international normative body and/or a national policymaking process recommends the use of a new method or strategy for HIV prevention for the population group enrolled in the trial, the presumption is that all trial participants should be ensured access to the method. Any departure from this recommendation must be clearly and persuasively justified on scientific and ethical grounds in the study protocol.
2. In settings in which high-quality prevention services are available in the community, it may be appropriate to provide access to new prevention tools either by direct provision at the trial site or by referral. If participants receive access to new prevention tools through referral, researchers and trial sponsors must use a system of active referrals to monitor access and to ensure quality care. Consistent with the commentary to guidance point 13, participants agreed that sponsors need not always provide prevention methods directly. Access to new tools could be achieved through referral to existing high-quality HIV prevention and care services rather than through direct provision by the trial.

3. It is the responsibility of the researchers and trial sponsors to ensure that new HIV prevention tools included as part of the standard prevention package are made available at no additional cost to study participants. The meeting participants agreed that to protect participant safety and maximise benefit, trials must cover the cost of the service as necessary, actively support referrals and ensure suitable levels of quality (Philpott et al., 2011, p. 246).

However, some of these criteria may result in similar ambiguities as guidelines, for example, criterion 1 requires international normative body and/or a national policymaking process.

Some trial implementers may wait for national guidelines before offering newly validated tools while others may offer prevention interventions based on international normative body approval. There is also little direction on how to ensure access to prevention interventions in circumstances where they are not available in the public healthcare sector and where sponsor funding policy prohibits the provision of such interventions (cf. UNAIDS/AVAC, 2011).

Meeting delegates also developed a set of seven questions to guide stakeholder decision-making during stakeholder consultations on standards of prevention (when regulatory approvals are pending). These questions consider the evidence to support the safety and scientific validity of the intervention; pragmatic/logistical considerations regarding availability and access to the intervention; and scientific design/statistical considerations. The specific questions follow:

1. What is the strength of evidence for efficacy/effectiveness of the new HIV prevention tool, including:
 - a. the point estimate and confidence limits for any estimate of effect;
 - b. the consistency of the data across different trial sites (contexts) and in different study populations; and
 - c. the number and type of clinical trials demonstrating an effect.
2. Has the efficacy/effectiveness of the new HIV prevention tool been demonstrated in comparable populations and for comparable modes of transmission?
3. Are there any safety concerns or other unanswered questions that could question the appropriateness of the new HIV prevention tool for the trial participants (e.g., antagonistic interactions with other components of the prevention package (cf. Dawson, 2012), concerns about frequency or duration of use, or cultural practices that could affect safety)?
4. Have the safety and efficacy or effectiveness data been reviewed and accepted by experts other than the trial investigators?
5. Is there general agreement in the public health community that the new HIV prevention tool would likely provide some protective benefit for the population enrolled in the trial?
6. Will it be feasible to provide trial participants with the new HIV prevention tool given local availability and accessibility, manufacturing and importation restrictions, or other relevant factors?

7. Will adding the new method undermine the trial's ability to isolate the efficacy of the HIV modality being tested? (Philpott et al., 2011, p. 246)

In circumstances where a newly validated prevention intervention is not included in the standard of prevention of trials, research stakeholders (including researchers, sponsors, national government, and community advocates) should develop a communication strategy (cf. UNAIDS/AVAC, 2011) to explain the clinical, scientific, and/or ethical justifications for not including the prevention tool in the standard prevention package (Philpott et al., 2011).

These criteria expounded by meeting delegates for consideration by stakeholders in determining the enhancement of the prevention package consider complicated statistical and scientific design issues, difficult for those without technical expertise (Haire et al., 2013; Koen et al., 2013) and require stakeholders to determine agreement among experts, which is difficult to achieve and evaluate (National Bioethics Advisory Commission, 2001).

3. The good governance model for stakeholder consultation

Stakeholder consultation is often recommended as a mechanism for decision-making in ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Further, it is recommended that trials should not be conducted until agreement has been reached on key ethical and scientific design issues, including the standard of prevention, (UNAIDS/WHO, 2012). However, guidance (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) provides no direction on how to operationalise such consultations (Philpott et al., 2011) and is not consistently explicit about which stakeholder groups should be consulted and at what points in the trial process.

The good research governance model (Tarantola et al., 2007) spells out a process for operationalising stakeholder consultations. The rationale for selecting this model is that it has informed the drafting of UNAIDS/WHO (2012) and UNAIDS/AVAC (2011) guidelines, has been applied to issues of care and treatment in HVTs, and its authors contend that it can be adapted for standard of prevention decision-making (Tarantola et al., 2007).

The good research governance model is the result of several consultations held by the WHO and UNAIDS that aimed to map out current guidance and approaches being applied in practical field situations, define obligations to provide care as well as constraints to the

provision of care and treatment in the context of vaccine trials, and identify potential creative mechanisms and approaches to the attainment of the highest possible synergy between scientific quality, outcome of research, and protection of trial participants (Tarantola et al., 2007, p. 4863).

There are different principled approaches to making decisions about obligations to participants in clinical trials including distributive justice (which focuses on the outcome) and procedural justice (which focuses on the process) (cf. Daniels, 2004). Ethical decision-making in research requires a deliberative process (HPTN, 2009). Daniels (2004) argues that outcomes arrived at through a fair deliberative process are likely to be perceived to have moral legitimacy. Social psychological research also suggests that people's perceptions of procedural fairness impacts on their evaluation of the outcome, that is, people are more willing to accept decisions if they believe that they were reached through a fair process, even if the outcome is not personally favourable (Tyler, 2000).

As mentioned above, one model for making procedural decisions in the context of HIV vaccine research is the good governance model (Tarantola et al., 2007). The good governance model proposes to involve all research stakeholders, including the community, in a structured, participatory and transparent decision-making process, that will allow agreement (cf. UNAIDS/WHO, 2012) to be reached on core obligations in settings where HVTs are planned (Tarantola et al., 2007). It identifies the ethical goal of such consultation as ensuring that the needs and legitimate expectations of trial participants are appropriately met, obligations towards them are delivered and, as a result, ethical research is facilitated in the interest of public health (Tarantola et al., 2007, p. 4863). The need to involve all research stakeholders in a transparent and deliberative decision-making process can also be justified on the basis of ensuring a fair process and is in line with the philosophical principle of respect for communities (cf. Weijer et al., 1999). In justifying the need for a decision-making model, Tarantola et al. (2007) argue that while ethical principles, like beneficence and reciprocal justice, obligate sponsors and investigators to provide care, treatment and prevention, these ethical principles are not always easy to apply. Further, Tarantola et al. (2007) contend that while ethics guidelines have also been developed to address key ethical complexities, they are often inconsistent and ambiguous (as discussed in Chapter 3).

The purpose of good research governance is two-fold. Firstly, as a process it aims to (i) ensure participation in decision-making, transparency and mutual accountability and (ii) document terms of agreement and responsibilities prior to initiation of the trial (Tarantola et al., 2007). Secondly, as an outcome it aims to (i) ensure compliance with international and national scientific and ethical standards and (ii) achieve a fair balance between community expectations and the provision of services to trial participants.

This model identifies a comprehensive list of research stakeholders who should be included in decision-making, namely: volunteers, trial participants, communities, researchers, funders, sponsors, health systems, employing organisations, community-based organisations (CBOs) and NGOs, care organisations, responsible care professions, regulatory authorities and RECs. According to Tarantola et al. (2007) these stakeholders must consider four questions in their deliberations, namely:

1. who should benefit from care, namely, potential trial participants excluded from a trial, enrolled participants, and/or other community members?;
2. what type of care should they receive, namely, diseases targeted specifically by the vaccine being studied, diseases diagnosed as part of the trial design, diseases unrelated to the purpose of the trial?;
3. what level of care should they receive, where level of care refers to the array of diagnostic, therapeutic and monitoring procedures relevant to a particular type of care?; and
4. who should bear the cost of providing care?

In addition, Tarantola et al. (2007) stipulate that four sets of criteria (normative, factual, evaluative and prospective) should be considered in decision-making. Firstly, *normative criteria* include established international, national and local norms and standards. Here stakeholder decisions should take into consideration ethics guidelines, sponsor and government policies, norms for scientific and ethical review, research governance and regulatory processes, guidelines on transparency and mutual accountability, national norms and practices regarding effective participation in decision-making as well as the requisite knowledge and skills that consultation participants should have in order to make effective contributions to a fair decision-making process.

Secondly, *factual criteria* include consideration of all the background evidence relevant to decision-making, including scientific and technical validity of the research design, the burden of the target disease, the required care and treatment necessary to satisfy study design requirements, ensuring participant safety during the study, existing and new collaborative partnerships, community expectations, and other context-specific considerations.

Thirdly, *evaluative criteria* consider expectations and the effectiveness of policies, structures and services, including technical feasibility of care and treatment options, costs and cost-effectiveness, national priorities and equitable access, and attention to vulnerable populations.

Finally, *prospective criteria* are concerned with projection of resources, mechanisms, resource needs and impact for each optional approach, including estimating the resources required for each approach and who will pay for them, who will manage resources, the sustainability of approaches post-trial, impact on existing health systems, impact on disease burden, social benefits, monitoring and accountability, communication and community involvement, establishing a precedent, and review.

Can this model be applied to standards of prevention? While the model has been proposed for setting standards for care and treatment in HIV vaccine research, the authors articulate that standards of prevention form an integral part of the study protocol. As for standards of care and treatment, these should be established through broad-based stakeholder consultation. The model proposed for setting standards of care and treatment may prove a useful tool adaptable to achieve this aim (Tarantola et al., 2007, p. 4865). A procedural approach focused on structured negotiating processes was also perceived as the optimal strategy for addressing several contentious issues including evolving standards of prevention, by participants at a UNAIDS workshop (Hankins et al., 2009). However, there are no published reports of adaptations of this model to standards of prevention. The authors justify their focus on care and treatment by arguing that prevention standards are commonly defined in the scientific design of vaccine trials whereas access to care is often insufficiently defined (Tarantola et al., 2007). However, in a review of two trial protocols (see Chapter 7), the standard of prevention was only explicitly defined in one protocol in terms of study design. Further, even when standards of prevention are defined in protocols, ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) require that all research stakeholders should

be consulted on the standard of prevention and there are few sets standards for making decisions (cf. Essack, Slack, et al., 2010).

3.1 Applying the four questions to standards of prevention

The first question refers to who should benefit from care, namely, screen-outs, enrolled participants, and/or other community members. This is also an important consideration for standards of prevention, that is, who should receive prevention methods, and is especially critical given that guidelines are generally silent on this issue (see Chapter 3).

The second question considers what type of care they should receive, namely, diseases targeted specifically by the vaccine being studied, diseases diagnosed as part of the trial design, or diseases unrelated to the purpose of the trial. This question does not map neatly onto standard of prevention considerations and will need to be adapted because, by definition, the standard of prevention refers to the prevention package provided to all participants in a trial to lower their risk of HIV (the target disease). Therefore, of particular concern is the question of which HIV prevention methods should be included in the standard of prevention package, including the incorporation of newly validated methods in the prevention package. This is considered a burning issue in standards of prevention (see Chapter 5). So, for this question it would be more appropriate to consider which HIV prevention methods should be provided to each moral group identified in question one above.

The third question refers to what level of care they should receive, where level of care refers to the array of diagnostic, therapeutic and monitoring procedures relevant to a particular type of care. Here this question could be easily adapted to consider the level of HIV prevention interventions in terms of diagnostic, therapeutic and monitoring procedures for each type of HIV prevention method.

The final question regarding who should bear the cost of providing care, is also applicable to HIV prevention, a question which is considered particularly contentious (see Chapter 5).

Stakeholder consultations on standards of prevention should therefore consider:

- (1) *Who* should receive HIV prevention interventions?
- (2) *Which* HIV prevention interventions should they receive?
- (3) *What* level of HIV prevention should they receive?

(4) *Who* should bear the cost of providing HIV prevention interventions?

Table 1 provides a decision-making matrix that considers these four questions as applied to standards of prevention. The left column of Table 1 addresses questions one and two. The column on the right deals with questions three and four, and some selected criteria for consideration. These questions will have to be addressed for each eligible moral group and applied to each HIV prevention intervention during decision-making, making it a potentially cumbersome exercise given the various stakeholder groups involved.

Table 1.

Decision-making matrix adapted from Tarantola et al. (2007)

Decisions on responsibilities for prevention in the context of vaccine trials	
HIV prevention interventions for:	Questions to consider for each moral group:
1. Trial participants	1. What HIV prevention interventions should be provided (including consideration of newly validated interventions)?
2. Participants who are screened out	2. For how long? (feasibility study, phase I, II and III, post-trial)
3. Partners of participants	3. Who will deliver HIV prevention interventions?
4. Families of participants	4. What prevention will be offered through existing services?
5. Host communities	5. What are government and sponsor policies on the standard of prevention?
	6. Who will provide the resources?
	7. Who will administer the resources?
	8. What will be the monitoring and accountability mechanisms?
	9. What will be the complaint and arbitration mechanisms?
	10. When, under what conditions and how will standards of prevention be re-evaluated?

The value of this framework in relation to ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) is evaluated below.

3.1.1 Who should receive HIV prevention interventions?

Ethics guidance (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) varies in identifying eligible groups for prevention services. While all agree that participants should receive HIV prevention interventions, there is inconsistency on whether screen-outs, participants/partners, and/or host communities should get access to HIV prevention interventions. Therefore, this model will be useful in helping to clarify who, apart from trial participants, should receive prevention interventions, what prevention interventions they

should receive, and how these prevention services should be accessed (on-site provision versus referral) by other eligible populations. Ethics guidance (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) does not provide adequate direction on these issues as described in Chapter 3.

3.1.2 Which HIV prevention interventions should be provided?

The prevention interventions offered to participants in HVTs is a somewhat controversial topic. Ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) have established substantive standards and spell out the components of prevention that should be ensured for trial participants. However, all guidelines endorse consultation with stakeholders, including the community, regarding the HIV prevention interventions that should be ensured (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). There is potential for conflict between substantive and procedural norms, as detailed in Chapter 3. Given that one purpose of the model is to ensure compliance with international and national scientific and ethics standards, consultations on what should be provided to participants seem superfluous given that these are already established in guidelines. Further, consultation on what to provide may result in several outcomes, some more ethical than others, namely, it may ratchet up the standard of prevention, it may endorse the current substantive standard, or it may actually undermine the substantive standard that this package be state-of-the-art (Essack, Slack, et al., 2010; Haire et al., 2012). It appears as though the substantive ethical standard and the procedural requirement for consultation are based on different ethical principles, namely, beneficence/non-maleficence and respect for communities, which may be in tension with each other when making decisions. It is also unclear about how best to resolve these tensions.

It is considered unethical to withhold prevention services from trial participants that they could obtain outside the trial (Macklin, 2009). However, neither the ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) nor the model provide any guidance on what to do if the community argues for a publically available prevention service (e.g., VMMC) not to be provided in the trial due to strong religious and cultural objections. Beneficence (and respect for the autonomy of individual participants) would imply that researchers should offer these services to participants. At the same time, if we are to take seriously the principle of respect for communities (Weijer, 1999), then these services should not be offered to participants. However, the latter position opens researchers to criticism for putting community concerns ahead of concerns about individual participants.

3.2 Strengths and weaknesses of the model

This model allows for deliberative decision-making that considers many relevant criteria, especially pragmatic consideration about how best to implement prevention services. Further, this model is helpful in identifying exactly which moral groups are entitled to which HIV prevention interventions. Apart from obligations to trial participants, what is owed to screen-outs, partners and the host community is not clearly articulated in guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

Unlike some ethics guidelines (MRC, 2003; UNAIDS/WHO, 2012), it is not left to the discretion of the reader as to who should be involved in consultations. Nonetheless, it may be impractical and infeasible to involve each of these stakeholders on every decision, for every clinical trial (cf. Koen et al., 2013; McGrory et al., 2010).

Some authors have cautioned that in the absence of clear norms, consultation using this structured approach to consensual decision-making to clarify core obligations, merely delegates the difficult struggle with norms and standards to consultative meetings (Stobie & Slack, 2010, p. 151). For example, determining which moral groups are entitled to standards of prevention is a normative undertaking best addressed by normative philosophical analysis, rather than via stakeholder consultation. Canvassing the opinion of stakeholders is morally respectful and not morally definitive (Essack, Slack, et al., 2010; Grady et al., 2008; Slack & Stobie, 2010). So, while consensus may be an important tool for making procedural decisions, these decisions should be made in a way that does not undermine substantive norms and standards.

This model lacks theoretical coherence. While it seems to resonate with the fair process approach (Daniels, 2000; 2004), this is not specified in the model. Unlike this model, the fair process approach is only used when there is a lack of set standards, and consultation would not be required to determine what to include in the package because there is already an established substantive standard. The ethical rationale for consultation is also not clear, but it appears congruent with the principle of respect for communities (Emanuel et al., 2004; Weijer, 1999).

4. Summary

Making decisions about the prevention services to provide to trial participants is complex and while guidelines provide some direction on how decisions should be made (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), these recommendations are vague and the processes necessary to operationalise guideline recommendations are not delineated. Some frameworks have been developed to facilitate decision-making about adding new tools to the standard of prevention package in a way that clarifies broad concepts such as scientific validity and regulatory approval (Jay et al., n.d.; McGrory et al., 2010; Philpott et al., 2011), and to operationalise ethics guideline recommendations for stakeholder consultation (Tarantola et al., 2007). While these frameworks offer detailed and helpful direction in operationalising recommendations, in some instances, e.g., feasibility determinations, they are subject to the same flaws as guidance. Further, these frameworks have not been piloted or evaluated for use as tools in standard of prevention decision-making. Empirical data on the implementation of these frameworks in HVTs and other prevention trials may help illuminate the pragmatic value of such frameworks, and identify how they could be strengthened.

The ensuing chapter provides an overview of the debates and complexities regarding standards of prevention, including in relation to norms in ethics guidelines.

CHAPTER 5

REVIEW OF DEBATES ON THE STANDARD OF PREVENTION

As already shown, the standard of prevention is a prominent ethical concern within the context of HIV prevention trials and has become a recent topic of intense debate and consultation (e.g., Essack, Slack, et al., 2010; Haire et al., 2013; Macklin, 2008; Philpott et al., 2011). Much of this tension emanates from standard of prevention norms outlined in ethics guidance (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) reviewed in Chapter 3. Further, the ethical rationale for providing HIV prevention interventions to trial participants remains unsettled, the decision-making process is fraught with gaps and complexities, and there are several other objections to providing participants with a state-of-the-art standard of prevention. This chapter reviews the debates regarding standards of prevention and the objections to providing a state-of-the-art standard of prevention to trial participants. It concludes with a review of previous empirical research and situates the present study within the empirical literature on standards of prevention.

1. Standard of prevention norms in ethics guidelines

Relevant ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) on standards of prevention in HVTs were reviewed in Chapter 3. These guidelines assert that participants should be provided with access to “optimal” (MRC, 2003) or “state-of-the-art” (UNAIDS, 2012; UNAIDS/AVAC, 2011) HIV risk-reduction interventions. However, some contend that the “state-of-the-art” standard may be too aspirational and not practically feasible (HPTN, 2009; Macklin, 2009; Rennie & Sugarman, 2010) especially in resource-constrained contexts with limited access to high quality prevention modalities (Macklin, 2010). It has been argued however, that the state-of-the-art standard is “an ethical aspiration, rather than an unwavering mandate” and that in circumstances where less than a state-of-the-art package is provided to participants, “this deviation must be strongly justified by a higher, competing obligation” (DAIDS, 2010, p. 10). Given that ethical aspirations are considered morally praiseworthy or commendable rather than ethically obligatory (cf. Rennie & Sugarman, 2010), it is unclear why exceptions would require a strong ethical justification, nor which competing obligations would be considered as validly trumping state-of-the-art requirements.

Ethics guidelines also recommend inter-stakeholder collaboration, and numerous engagement activities, to ensure access to the highest standard of prevention (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). They make a range of recommendations about the standard of prevention in trials, including what should be declared in protocols and ICFs; which prevention interventions should be included in the prevention package; that prevention interventions should be monitored and documented; and about how decisions should be made on what to provide and when to add new tools to the prevention package. These recommendations have been argued to set a very high standard (Essack, Slack, et al., 2010). Complexities with specific standard of prevention norms in HVT-specific ethics guidelines are also explored throughout this chapter.

2. The ethical rationale for standards of prevention

The ethical rationale underpinning the provision of HIV prevention interventions to participants is not settled. There is no published literature arguing that HIV preventive interventions should *not* be provided to trial participants. There is wide ethical consensus that participants should be provided with prevention interventions to reduce their risk (Macklin, 2008; Slack et al., 2000; Rennie & Sugarman, 2010). However, various justifications for providing participants with a standard of prevention have been offered thus far.

One rationale is that since participants in late-phase trials are at high-risk for HIV infection, they should be provided with prevention interventions to help reduce their risk (Essack, Slack, et al., 2010; MRC, 2003). Another rationale is that factors that place participants at high risk for HIV also increase their vulnerability, and that there is an ethical obligation to protect the vulnerable (de Zoysa et al., 1998). Further, the experimental nature of HVTs, the fact that some participants receive placebo, and that HIV is incurable, all underlie obligations to provide prevention interventions to trial participants (IAVI, 2005). Commentators have noted that standard of prevention obligations are founded on the provision in the Declaration of Helsinki that the researcher's primary obligation to minimise risk for participants is paramount over consideration of future beneficiaries of research (Haire et al., 2012). Finally, prevention services should be provided to participants in order for researchers to satisfy their responsibilities as articulated in ethics guidelines (cf. de Bruyn et al., 2009).

2.1 Bioethics frameworks and the standard of prevention

McGrory et al. (2010) report on a review of what various bioethics frameworks would outline as researchers' HIV prevention responsibilities, including principlism, standard of care, therapeutic obligation and equipoise, and duty of rescue. Lie et al. (2006) explore three potential ethical rationales for the provision of VMMC in HIV prevention trials, including behavioural disinhibition, reciprocal justice and the Good Samaritan argument. These potential ethical rationales for the provision of HIV prevention interventions to trial participants are outlined below.

2.1.1 Principlism

The first ethics framework from which potential ethical rationales for the provision of HIV preventive methods to trial participants are derived, is principlism. After a series of research abuses, the US government established a commission in the 1960s mandated to develop guidelines for the ethical conduct of research with human participants. The resultant document, the Belmont Report, expounded three ethical principles for research, namely, respect for persons, beneficence and justice. These principles, or 'prescriptive judgments', were envisaged to provide a moral framework to guide the ethical conduct of research with human participants and resolve any resultant ethical dilemmas (NCPHSBBR, 1979).

Respect for persons requires that all participants be treated with respect, that individuals be treated as autonomous human beings, and that those with diminished autonomy are entitled to extra protection (NCPHSBBR, 1979). Beneficence/non-maleficence requires that all potential risks to participants be minimised and potential benefits maximised (NCPHSBBR, 1979).

The principle of justice or fairness requires that the benefits and burdens of research are equitably distributed (Wassenaar, 2006) and that study participants and trial communities are not exploited (McGrory et al., 2010).

Beneficence and non-maleficence have been offered as ethical rationales for providing prevention interventions to participants. These principles require that researchers recognise the potential vulnerability of trial participants and then design trials to minimise this risk and maximise benefits (McGrory et al., 2010; Slack et al., 2000). It is often assumed that this translates to a duty to protect participants' welfare and 'provide services known to reduce the risk of HIV infection and accepted as the standard of care' (de Zoysa et al., 1998, p. 571). Further, researchers cannot withhold HIV prevention interventions from participants if they

exist within the trial community (Macklin, 2009). Similarly, UNAIDS/WHO (2012) guidelines assert that beneficence and non-maleficence underpin the obligation to provide prevention interventions to participants. These principles obligate researchers and sponsors to reduce the risk that any trial participant will acquire HIV infection during a biomedical HIV prevention trial (UNAIDS/WHO, 2012, p. 45).

However, there are limits to this obligation and not all ethicists concur that it is the principle of beneficence that compels researchers to provide participants with access to all established effective HIV prevention methods (cf. Lie et al., 2006; McGrory et al., 2010; Philpott et al., 2011). Firstly, rather than a risk of study participation, HIV acquisition may occur due to behavioural, contextual or structural-level risks (cf. Haire et al., 2012). It has been empirically shown that HIV incidence among trial participants tends to decrease because of sustained risk-reduction counselling and provision of effective HIV prevention tools (UNAIDS/WHO, 2012, p. 12). Secondly, the metaethical principle ofought implies canø dictates that researchers are morally required to do what they are capable of doing, or what is reasonable to ask (van de Graaf & van Delden, 2009, p. 37). This means that ethical standards must be feasible or implementable in practice (van de Graaf & van Delden, 2009, p. 37). A case in point is that while many ethicists contend that VMMC should be provided to participants when researchers can afford to do so, some argue that this obligation does not extend to circumstances where circumcision is not yet established and accepted by the local community (HPTN, 2009; McGrory et al., 2010).

Another rationale for providing preventive interventions is based on reciprocal justice where participants are rewarded with preventive interventions because the trials in which they enrol contribute social benefits, such as improved prevention methods (Lie et al., 2006). Here researchers would be required to evaluate the overall risks and benefits of participation and demonstrate that the provision of preventive interventions is fair compensation for participation (Lie et al., 2006). Since trial participants give more of themselves it is suggested that they do indeed qualify for special treatment in the form of access to services or benefits not available to others ó researchers obligations to the larger society do not surpass their responsibilities to individual participants (Heise & Wood, 2005).

Still, Tarantola et al. (2007, p. 4863) argue that while ethical principles, like beneficence and reciprocal justice, create certain obligations on researchers, sponsors and public health

authorities... these obligations are poorly defined in practical terms, inconsistently understood or inadequately applied.ö

2.1.2 Behavioural disinhibition

Behavioural disinhibition/risk compensation captures the potential for participants to place undue faith in the protective effects of the intervention or technology under studyö and compensate by increasing their risky behaviour (Woodsong et al., 2012, p. 786). Such risk compensation may occur due to three fundamental misconceptions: an overestimation of the potential effectiveness of the experimental HIV prevention intervention, belief that one is assigned to the experimental arm, and that prevention trials are intervention programmes (Cassell, Halperin, Shelton & Stanton, 2006; Chakrapani, Newman, Singhal, Nelson & Shunmugam, 2013; Gray et al., 2013). Therefore, an obligation to provide preventive interventions could be justified because of the potential for increased risky behaviour in such trials (cf. Lie et al., 2006). Although, HIV incidence typically decreases among HIV prevention trial participants, some increases in risk behaviour have been observed in HIV vaccine research (Chesney, Chambers & Kahn, 1997). Still others have argued that there is little evidence for behavioural disinhibition (Slack et al., 2000; Lie et al., 2006) and that limited data from HIV vaccine and other HIV prevention trials has generally not indicated any overall increase in risk behaviour amongst trial participants (Agot et al., 2007; Gray et al., 2013; Guest et al., 2008). Recent research also found no evidence for risk compensation among participants in an HIV vaccine efficacy trial conducted in South Africa (Gray et al., 2013). Further, participants are counselled at every study visit on how to reduce their risk. It is also emphasised during counselling that participants should not assume that they are protected from HIV infection given that the product is experimental and assignment to the experimental and control arms is double-blinded (cf. MRC, 2003). Therefore, it is argued that the potential for behavioural disinhibition provides a weak justification for the provision of prevention services (Lie et al., 2006).

2.1.3 Standard of care

A third potential rationale for providing participants with HIV prevention interventions is that it is ethically abhorrent for trial participants to receive care or prevention services not on par with the established standard of care (McGrory et al., 2010). However, there is disagreement

on whether the established standard of care should reflect the best-proven interventions available globally or whether this should be locally defined⁶ (Dawson, Klingman & Marazzo, 2014; Haire et al., 2013; McGrory et al., 2010). Each has its own drawbacks. Most ethicists and researchers agree that providing the locally established standard of care which may comprise only a few, if any, prevention interventions is wholly inadequate (McGrory et al., 2010). At the other extreme, providing an internationally established state-of-the-art standard of prevention may not be feasible in some developing country contexts (Macklin, 2010; Rennie & Sugarman, 2010). Determining the appropriate standard of prevention is complex because entitlements to health services vary by country, and even in well-resourced countries, participants are not entitled to all available, effective (or state-of-the-art) interventions because justice necessitates establishing priorities (Emanuel et al., 2004, p. 933). While providing a locally relevant standard of prevention is argued to compromise generalisability to other contexts (Haire & Jordens, 2013), results that are irrelevant to the host community are unethical (Emanuel et al., 2004). As long as the study is socially valuable (especially to the host community), providing a standard of prevention beyond that to which participants are entitled or that are feasible and sustainable may be unethical if it undermines scientific validity or makes the results irrelevant to the community (Emanuel et al., 2004, p. 933).

In their review of HIV prevention trials, Padian, McCoy, Balkus and Wasserheit (2010a) found that most of the services provided to participants in the control arm were not sustained post-trial nor were there plans to do so. Given that the experimental product is not compared to the standard in the local setting, this compromises the study methodologically (Padian et al., 2010a). These authors suggest that the standard of prevention offered in trials should be on par with the established local standard for the provision of a feasible, well documented plan for the sustainability of proposed new services as a measure of both the ethical and methodological appropriateness of interventions in control groups (Padian et al., 2010b, p. 2299). On the other hand, it is argued that even if the ethical criterion of sustainability (Padian et al., 2010b) is not realised post-trial, the immediate potential benefit of reduced HIV infection risk for participants (and their sexual partners) is a legitimate trial-related benefit (Haire et al., 2013), that may have ongoing impacts on HIV incidence (Haire & Jordens, 2013). Another suggestion is to provide as high a standard of prevention as possible

⁶ Readers are referred to Alex London's seminal work (London, A. J. (2000). The ambiguity and the exigency: clarifying 'standard of care' arguments in international research. *Journal of Medicine and Philosophy*, 25(4), 379-397), which attempts to disambiguate the concept of a 'standard of care'.

while ensuring that this is not infeasible for researchers, or unachievable and/or unsustainable in the local context (HPTN, 2009; McGrory et al., 2010). Further, if the local standard of care is poor, efforts should be made to ratchet up available services (Shapiro & Benatar, 2005).

2.1.4 Therapeutic obligation and clinical equipoise

The therapeutic obligation and clinical equipoise may also ground researchers' obligations to provide participants with a standard of prevention (McGrory et al., 2010). The therapeutic obligation compels physicians (and by extension physician-researchers) to act in their patients' best interests (McGrory et al., 2010). Clinical equipoise requires genuine uncertainty about whether an experimental vaccine is better or worse than the existing standard of care (Haire & Jordens, 2013; McGrory et al., 2010). Given the uncertainty about the experimental intervention coupled with obligations to act in participants' best interests, it follows that researchers are obligated to provide participants with effective HIV prevention interventions. However, some commentators contend that the concept of clinical equipoise is itself defective, incoherent (Miller & Brody, 2003, 2007) and irrelevant (Veatch, 2007). Since researchers are not primary-care physicians (Miller & Brody, 2003, 2007) and services provided in HIV prevention trials differ from medical care typically received by patients, the therapeutic obligation may not be a sound argument for framing researchers' HIV prevention responsibilities to trial participants (McGrory et al., 2010).

2.1.5 The duty of rescue

Like the principle of beneficence, the duty of rescue (or Good Samaritan argument) requires that potential benefits are maximised and potential risks minimised (McGrory et al., 2010). Therefore, the provision of preventive measures could be morally justified based on the fundamental ethical requirement for any person to do what they can to help others in need (Lie et al., 2006, p. 523). It follows that researchers are obligated to provide participants with some care beyond that required for the conduct of the study, although this obligation too has limits (McGrory et al., 2010). This ethical obligation implies that certain scientific and logistical considerations must be satisfied such that the intervention should have proven effectiveness and can be justified in terms of acceptable and reasonable costs in relation to the magnitude of benefits that one could expect (Lie et al., 2006). If the prevention tool is both effective and economical given the context, then researchers will be ethically obligated to promote it and perhaps even ensure access to it as part of trial costs (Lie et al., 2006). However, the availability of a cost-effective prevention tool will likely create an even

stronger moral obligation on health authorities to include this tool as part of the public healthcare system; if the prevention tool is already in the public domain researchers would be obliged to provide information about the tool, remove barriers to access, and encourage participants to access it (Lie et al., 2006). As long as the costs of providing such preventive care do not compromise the trial, there is no compelling reason why the researchers do not have an obligation to provide as many additional medical and social services to study participants as possible (McGrory et al., 2010, p. 11).

In summary, all commentators agree that there is an ethical mandate to provide participants with preventive interventions. However, this obligation is derived from various ethical principles and frameworks and the ethical reasoning informing guidelines and recommendations on the standard of prevention is not clear (McGrory et al., 2010) or explicit. Even within one framework, e.g., principlism, there are different potential rationales for providing preventive interventions to participants. Ethics guidelines and frameworks can provide broad principles but rarely provide a one size fits all set of recommendations on the types and levels of prevention and care services within individual research trials (McGrory et al., 2010, p. 11).

3. Complexities regarding the standard of prevention

There is little clarity about how decisions should be made about standards of prevention in trials. The decision-making process is unclear (Cohen, Mastroianni & Macklin, 2014; Essack, Slack, et al; 2010; Philpott et al., 2011); the incorporation of newly validated prevention interventions in the standard of prevention is fraught (Cowan & Macklin, 2014; Dawson, 2012; Haire et al., 2012; Macklin, 2012; Philpott et al., 2011; Rennie & Sugarman, 2010); and there is little certainty about exactly which stakeholders are ethically responsible for ensuring implementation of the standard of prevention and covering the costs of prevention interventions (Essack, Slack, et al., 2010; Macklin, 2008). These decisions are complicated by many factors including vague guidance, a paucity of (evaluated) operational frameworks for decision-making, and an absence of established standards for decision-making.

It has been mentioned that there is increasing consensus regarding the provision of state-of-the-art HIV prevention interventions in trials (Macklin, 2008). However, debate remains about what services should be included in the package of prevention. Currently, male and female condoms, VMMC, STI diagnosis and treatment, education and risk-reduction

counselling, PEP, the provision of clean needles and medical substitution therapy, treatment as prevention, and PrEP are available tools for HIV prevention (see Chapter 2). To add to the current prevention arsenal, many new technologies are being tested. Recent developments in HIV prevention research include positive trial outcomes for oral and topical PrEP and treatment as prevention, and while these findings are welcomed and celebrated, they create ethical and scientific challenges for future HIV prevention trials.

While there is broad agreement (McGrory et al., 2010; Slack et al., 2000; UNAIDS, 2000) that participants should receive access to certain HIV risk-reduction interventions (such as condoms, counselling and STI treatment), there has been some disagreement about obligations to ensure access to other interventions such as VMMC (cf. Lie et al., 2006; HPTN, 2009), PEP (UNAIDS, 2000) and PrEP (Cowan & Macklin, 2014; Dawson, 2012; Haire et al., 2012; Haire, 2014; McEnery, 2012; Sugarman & Mayer, 2013). Ambiguities in guidelines about what should be included in the prevention package are manifested in practice – the standard of prevention offered to participants in HIV prevention trials is variable (Haire & Jordens, 2013; Heise et al., 2008; Ngongo, Priddy, et al., 2012). A further complexity is that there are no established standards for decision-making (Kim et al., 2010) and variable standards have been used across trials and stakeholder groups (cf. Essack, Slack, et al., 2010; Haire & Jordens, 2013; Philpott et al., 2011).

As newly validated HIV prevention tools emerge, there has been increasing debate about whether they should be added to the standard of prevention, including whether a state-of-the-art package would include VMMC and a partially effective vaccine or microbicide if such methods are proven effective (Macklin, 2009). The requirement to provide access to all state-of-the-art prevention interventions has been argued as setting a very high standard (HPTN, 2009; Macklin, 2009) and as creating concerns about the feasibility of future trials (Macklin, 2008).

Ethics guidelines provide some direction on the addition of new prevention interventions to the prevention package. Firstly, new tools should be added when they are scientifically validated (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). A second criterion for adding new tools is approval by relevant authorities (UNAIDS/WHO, 2012) or national bodies for use (UNAIDS/AVAC, 2011). As described in Chapters 3 and 4, ethics guidelines do not outline the criteria for ‘scientifically validated’ or ‘approved by relevant authorities’

which is problematic because these conditions are defined differently by different regulatory and normative bodies (McGrory et al., 2010). For example, in terms of scientific validity, with VMMC normative bodies required evidence from three RCTs before issuing guidance but male condoms were recommended as an effective strategy based only on observational data (Philpott et al., 2011). In terms of normative/regulatory approval, some trials provided VMMC based on scientific evidence while others only included VMMC in the prevention package after the introduction of VMMC in national guidelines (Essack, Slack et al., 2010; Haire & Jordens, 2013). Furthermore, when considering whether a new prevention intervention is scientifically validated, the requirements for new tools far exceed what was previously accepted (Padian et al., 2008). For some tools, e.g., condoms and PEP, there is only data from observational studies yet for new tools the requirement is evidence from at least two RCTs. Regulatory requirements for two RCTs have been criticised as unduly delaying the introduction of effective prevention interventions in high-risk populations (Haire et al., 2012) although this was rebutted because it would be irresponsible (and arguably unethical) to provide prevention interventions to participants based on inconclusive evidence (Dawson, 2012).

Given the evidence for efficacy of PrEP (oral Truvada), in relation to the operational criteria for clinical validation (Jay et al., n.d.) and scientific validity (Philpott et al., 2011), PrEP can be considered scientifically validated. For this reason, it has been argued that PrEP should be included in the standard of prevention in future HIV prevention trials (Cowan & Macklin, 2014) or as an active comparator (Haire, 2014). Further, ō[w]ith the FDA now having approved PrEP for HIV prevention, under the UNAIDS guidelines there is a *prima facie* requirement to provide PrEP as standard of prevention, as PrEP clearly meets the definition of ōstate-of-the-art,ö having been approved by a normative bodyö (Haire, 2014, p. 6). However, while PrEP has been approved as an effective prevention strategy by the US FDA, it is yet to be approved in any other country in which trials were conducted (Haire, 2013; Hankins & Dybul, 2013). Denying participants access to a prevention intervention simply because it has not been registered in the country where they live, has been argued to be ethically problematic (Cowan & Macklin, 2014). However, it has also been argued that interventions should not be provided as part of the standard of prevention in trials when they have not been approved by national regulatory authorities (cf. Philpott et al., 2011). Disagreement on this issue is enabled by vague guidelines, for example, while Haire (2014) contends that there is a *prima facie* requirement to provide PrEP, she also notes (Haire, 2013)

that UNAIDS guidelines are ambiguous and it is not clear whether approval would be required from national authorities or whether any regulatory or normative body approval would suffice. Therefore, it is difficult to imagine that in contexts where PrEP is not approved, inaccessible, or cannot be reasonably procured (Jay et al., n.d.) that it could be considered unethical by UNAIDS ethics guideline standards not to provide this intervention to HVT participants.

These ambiguities on ethical concepts in guidance are further complicated by requirements that the prevention package be determined via a process of consultation with all research stakeholders (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), that trials should not be conducted unless all stakeholders agree on the standard of prevention before a trial commences (UNAIDS/WHO, 2012), and that the prevention package should be negotiated (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). It is specified that negotiations should consider the impact of enhanced standards of prevention on trial feasibility and the ability to isolate the effect of the experimental intervention (UNAIDS/WHO, 2012).

Several concerns have been raised regarding these procedural requirements. Firstly, guidelines do not provide direction on how to operationalise these decision-making mechanisms (Cohen et al., 2014; Philpott et al., 2011). Secondly, commentators have noted that these requirements present pragmatic complexities since many HIV prevention trials are designed well in advance of their implementation (Haire et al., 2013) and for multi-site trials, protocol development is often centralised (UNAIDS/AVAC, 2011). Therefore, extensive consultation and stakeholder input on the design of the standard of prevention may not always be possible, and is further compounded by low levels of literacy which may constrain discussions on standards of prevention (Haire et al., 2013). Thirdly, as identified in the review of standard of prevention norms in HVT-specific guidelines (Chapter 3) procedural requirements may conflict with substantive standards requiring access to state-of-the-art prevention interventions and in some instances this may undermine the substantive norm and lower the prevention package (Essack, Slack, et al., 2010; Haire et al., 2012). Similar tensions have been noted by Philpott et al. (2011) who recommend additional work in order to clarify how the substantive standard that the package be state-of-the-art (UNAIDS/WHO, 2012) relates to the procedural standards of consultation, agreement and negotiation.

In terms of the negotiation recommendation (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), theoretical concerns have been raised about how structural power inequities between communities and researchers, and between resourced and resourced-constrained contexts may limit the ability to negotiate (Haire, 2013; West Slevin, Ukpong & Heise, 2008).

Recommendations to negotiate have also been criticised as serving the interests of the research elite rather than communities (Haire, 2013) given their consideration of statistical, scientific and technical issues. Given these limitations, it has been recommended that standard prevention packages should be provided in line with clearly defined guidelines as a responsibility of researchers to the research participant. The utilisation of GPP (UNAIDS/AVAC, 2011) as a practice guide in the design and implementation of HIV prevention research is expected to better systematise community engagement and promote greater ownership of research by communities (Haire et al., 2013, p. 6). This recommendation, however, does not resonate with empirical findings that some standard of prevention recommendations outlined in GPP guidelines (UNAIDS/AVAC, 2011) are considered challenging to implement (Moorhouse et al., 2014).

As indicated in Chapter 4, another complexity relates to the resources to fund prevention interventions (Kim et al., 2010) and which stakeholders should pay for the provision of these interventions to participants (Macklin, 2008). It is argued that the burden should not fall on sponsors and researchers alone; nor is it affordable for poorly resourced governments on their own (Macklin, 2008). It is accepted that researchers are not solely responsible for meeting healthcare related needs of trial participants and while they are obligated to ensure access to adequate healthcare, this does not entail that researchers should provide it themselves (Heise & Wood, 2005, p. 35). However, who pays for prevention interventions is complex because it may be constrained by sponsor funding policies (Philpott et al., 2010; UNAIDS/AVAC, 2011) and the local healthcare context (Macklin, 2010). One suggestion has been to incorporate costs into budgets supported via public-private partnerships and that skilled negotiators be utilised in brokering such arrangements (Macklin, 2008). Ethics guidelines also suggest that researchers and sponsors should collaborate with host country governments to ensure access to the highest standards of prevention and care because these efforts should be envisaged as a shared responsibility (UNAIDS/WHO, 2012).

Considerations related to the local context of the planned HVTs have also been argued as important (Rennie & Sugarman, 2010), including feasibility, accessibility and sustainability

of the intervention. It has been argued that newly validated tools should not be added to the prevention package when they are not widely available in the host context, not approved by national regulatory bodies and not sustainable in the local context after the trial (cf. HPTN, 2009; Philpott et al., 2011). On the other hand, it is argued that the immediate potential benefit of reduced HIV infection risk for participants (due to the addition of a new prevention intervention), is a legitimate trial-related benefit (Haire et al., 2013). Finally, potential interaction effects between the vaccine and other prevention interventions require careful assessment (Dawson, 2012), and may also affect licensure of the experimental vaccine.

4. Objections to providing a state-of-the-art standard of prevention

There have been a slew of objections to ethics recommendations to provide access to all state-of-the-art HIV prevention interventions including that it sets the bar too high, introduces significant inequities between trial participants and communities, may result in undue inducement, and increased behavioural disinhibition (HPTN, 2009). Further, since large-scale efficacy studies are often conducted in developing country contexts where there is a high burden of disease, there is some concern that strict adherence to ethics guidelines may be challenging, given limited access to state-of-the-art prevention packages in these contexts (Macklin, 2010). Concerns regarding undue inducements, creating inequities between trial participants and communities, and the potential impact on trial feasibility are described below.

4.1 A state-of-the-art standard of prevention is an undue inducement

There is concern that a state-of-the-art standard of prevention will create an undue inducement to participate in trials (de Zoysa et al., 1998; HPTN, 2009; cf. UNAIDS/WHO, 2012). Undue inducements are offers of a desirable good in excess such that it compromises judgment and leads to serious risks that threaten fundamental interests (Emanuel, Currie & Herman, 2005, p. 337). Proponents of the argument that a state-of-the-art standard of prevention is an undue inducement suggest that offers of medical care, not generally available, may unduly influence people to participate in risky clinical research (HPTN, 2009). Similarly, it may be argued that providing participants with a comprehensive prevention package may serve to compromise participants' abilities to evaluate the risks of their participation. It is argued that offering an extensive array of HIV prevention methods when these methods are not generally available in the community may also constitute undue inducement to participate (HPTN, 2009, p. 44). However, some argue that undue

inducement should not be a concern in clinical research as long as RECs approve the research and the risks are reasonable in and of themselves (Emanuel, 2004; Emanuel et al., 2005). However, approval of research by RECs may not absolve the researcher of undue inducement concerns as RECs are sometimes not capacitated to evaluate risks competently (Martin, 2005; Milford et al., 2006). Others have contended that the provision of services and care beyond what is necessary to conduct the trial should not be understood as undue inducements because inducements are only “undue” and problematic when they are so attractive that they impair a volunteer’s ability to employ proper judgment and leads them to discount risks (Heise & Wood, 2005). Further, as with the provision of ART, it is plausible that access to benefits like HIV prevention interventions may be based on rational choice and are not evidence of distorted decision-making (Slack et al., 2005). Further, it is argued that “because there is not an enormous amount of risk associated with participating in HIV prevention trials, offering real benefits to participants is unlikely to constitute an “undue inducement” (McGrory et al., 2010, p. 29).

4.2 A state-of-the-art standard of prevention introduces local inequalities

If the state-of-the-art standard is benchmarked against international best practice, in some contexts, this standard would be higher than the available local standard. Providing HIV prevention strategies to trial volunteers when they are unavailable to the larger community in which the trial is situated, has been considered unethical and as creating “serious inequities between research participants and community members with similar needs” (HPTN, 2009, p. 46). However, the principle of reciprocal justice deems it appropriate that participants receive services that may not be available to the broader community (Heise & Wood, 2005). It is argued that researchers should always endeavour to minimise inequities but that such disparities exist in most contexts (Heise & Wood, 2005). Efforts to provide benefits and improve the lives of some (even if not all), is not morally problematic (Heise & Wood, 2005). National guidelines (MRC, 2003) also suggest that participants should receive services that they would not otherwise obtain and while this may introduce local inequalities, it reflects active protection and fair treatment of participants. This resonates with the position in UNAIDS/WHO (2012) guidelines that social justice concerns do not fully appreciate that “all scale-up programmes involve temporary inequalities in the community until universal access can be attained. Achieving a perfect system of equal justice is a long-term process” (p. 44).

4.3 A state-of-the art standard of prevention may negatively impact on trial feasibility

As described in Chapter 2, HIV prevention efficacy studies are conducted to determine whether the experimental prevention method can decrease the risk of HIV infection more than the standard of prevention provided to participants in both arms of the study (de Zoysa et al., 1998). In these trials, the primary endpoint is HIV infection. However, even in areas of high HIV incidence, HIV infection is a relatively uncommon occurrence (Lagakos & Gable, 2008). Therefore, prevention trials are often complex and expensive to conduct as they require enrolling and retaining several thousand HIV-negative participants over several years (Hankins, 2006). Furthermore, researchers are ethically obligated to provide all participants with prevention interventions to reduce their risk of HIV acquisition (MRC, 2003; UNAIDS/WHO, 2012; UNAIDS/AVAC, 2011) thus decreasing HIV incidence in both the experimental and control arms of trials (UNAIDS/WHO, 2012).

Clinical trials must demonstrate that the experimental intervention has a benefit above that of the risk-reduction methods being provided. The more effective the prevention package provided to participants, the lower the incidence, and the less power the trial has to detect beneficial effects of the experimental intervention (Lagakos & Gable, 2008). This is not a theoretical concern. For example, in the MIRA diaphragm trial, diaphragms plus condoms were compared against condoms alone. Since HIV transmission rates were similar in the intervention and control arms, it was interpreted widely that diaphragms were ineffective. A more correct interpretation was that they might have been equally efficacious as condoms, as condom use in diaphragm group was uncommon, despite encouragements for their use (Vermund et al., 2009, p. 271). In their review of 37 HIV prevention RCTs reporting on 39 unique interventions, Padian et al. (2010a) reported that nearly 90% of these trials produced flat results, many of which may be attributed to trial design and/or implementation issues. In many of the studies with no effect, the intensity of risk-reduction services offered in both arms is a key consideration with most of these studies providing a prevention package that exceeded the standard available in the local community (Padian et al., 2010a). This may dramatically reduce the ability to detect the effect of a new and effective intervention (Padian et al., 2010a).

As newly validated prevention interventions emerge, researchers worry that requiring a prevention package containing state-of-the-art methods will thwart their ability to obtain

meaningful results of trials (Macklin, 2008, p. 285). In order to counter such decreases in statistical power, trial sample sizes will need to increase, resulting in longer, more expensive trials (cf. Essack, Slack, et al., 2010; Haire, 2014). Trial implementers must consider how to incorporate new tools in their protocols, in a context of inflationary increases, resource-intensive trials, and diminishing investments (RTWG, 2013; 2014).

The standard of prevention may create tension between scientific validity and exploitation, that is, between a clinical trial's scientific aim to obtain meaningful results and ethical requirements to minimise risks and not withhold effective interventions from participants. Withholding proven interventions from participants (even if they are not available in the local context) may raise concerns about exploitation (MacQueen, 2011). However, enhanced prevention packages may result in futile trials and may undermine the real-world applicability of the data (Rennie & Sugarman, 2010). Furthermore, incorporating new prevention interventions in trials changes the questions that can be answered by the trial (Dawson, 2012). These tensions have been particularly pronounced in terms of decisions on evolving standards of prevention. On the one hand, protecting the welfare of trial participants is paramount and necessitates providing all validated prevention interventions. However, for research to be ethical it must produce scientifically valid and socially valuable results (Dawson, 2012; Emanuel et al., 2004). Therefore, any analysis of trial designs must consider the protection of participants in relation to the threshold at which the provision of enhanced standard of prevention packages invalidates trials (Emanuel et al., 2004; Essack, Slack, et al., 2010) and impedes the development of increasingly effective interventions (Sugarman & Grace, 2010). If the feasibility of obtaining meaningful results from the trial is adversely impacted by the addition of new HIV prevention methods, then the ethical obligation to provide all state-of-the-art methods is weakened because participants will be exposed to risks and inconvenience for no social benefit and valuable resources will be wasted (Emanuel et al., 2004; Essack, Slack, et al., 2010; Lie et al., 2006). Furthermore, the production of irrelevant research is both a scientific and ethical concern (Rennie & Sugarman, 2010, p. 812). However, the threshold at which adding new methods will invalidate trials has yet to be clearly defined and remains an important ethical undertaking (Essack, Slack, et al., 2010).

5. Previous empirical studies on prevention in HIV prevention trials

There has been some empirical investigation of the standard of prevention provided to participants in HIV prevention trials (Haire & Jordens, 2013), microbicide and diaphragm studies (Heise et al., 2008; McGrory et al., 2010) and HVTs (Ngongo, Priddy, et al., 2012).

5.1 Findings on standard of prevention decision-making

In terms of HIV prevention decision-making practices, findings reflect that variations in the standard of prevention across trials could be accounted for by several factors including local guidelines and standards; trial design considerations; the services and resources available in a local site setting; providers' knowledge, comfort, training, and beliefs; and when the study started (McGrory et al., 2010, p. 24). The Global Campaign for Microbicides⁷ (GCM) review of policies and guidance documents found that while only a few donor policies set a minimum standard of prevention for trial participants, there were many examples of where general policies or uncertainty about donor expectations influenced decisions about what care to provide trial participants including restrictions on HIV prevention interventions (Philpott et al., 2010, p. 223). For example, funding from the NIH prohibits the use of federal funds for the procurement of drugs or the provision of care not required for the scientific conduct of the trial or to ensure participants' safety (Philpott et al., 2011). Protocol omissions of strategies to ensure care services in HIV prevention trials in order to comply with sponsor funding policy have been identified in empirical studies (Philpott et al., 2010; Heise et al., 2008; Slack, 2014). In contrast, Haire (2013) found that donor policies positively influenced the provision of standards of prevention.

Interview data (Heise et al., 2008) suggest that external bodies like RECs and donors do influence aspects of the standard of prevention such as messages around condom use. For example, in one study, a US REC required that investigators add a statement to the consent form that, "the only way to prevent HIV/STIs is not to have sex" despite the fact that being sexually active was an eligibility criterion (Heise et al., 2008, p. 36). While ethics guidelines recommend consultations with stakeholders, including inputs from the community on standards of prevention prior to the initiation of the trial, Heise et al. (2008) found little evidence of this. Only one site consulted community members and advisory groups about the prevention services that should be provided to participants prior to study approval – mostly,

⁷ <http://www.global-campaign.org/>

inputs were obtained from communities after the study was approved (Heise et al., 2008). While there was little interrogation of why inputs from the community were rarely obtained prior to the approval of the study, the authors reinforced that the standard in ethics guidelines should be adhered to in that “community voices should be sought and integrated into standards of care decision-making at every stage of the trial design and implementation” (Heise et al., 2008, p. 67).

5.2 Findings on standard of prevention implementation practices

The GCM mapping study found that participants received intensive quality counselling, unlimited free male condoms and quality STI services. However, female condoms were not actively promoted with some site staff reporting perceptions that female condoms were expensive and inaccessible (Heise et al., 2008). An abbreviated mapping study, also conducted by GCM, explored the HIV prevention services offered to participants across a wider range of HIV prevention trials including herpes suppression, PrEP and HVTs; 18 HIV prevention trials in total. Of these, three were HVTs (HVTN 204, HVTN 502 and HVTN 503) with HVTN 204 and HVTN 503 having trial sites in SA. In HVTN 204, the standard of prevention for all participants comprised male condoms, female condoms if available in the community, referral for STI treatment and clean needles if requested. In HVTN 502 (or STEP), the prevention standard included male condoms and STI treatment if indicated. HVTN 503 (or Phambili) provided the most HIV prevention interventions for trial participants including male and female condoms, treatment of STIs, STI treatment for partners, PEP and VMMC (CDC/GCM/UNAIDS, 2009). While there was some standardisation in terms of general categories like condom promotion and risk-reduction counselling, the type and intensity of prevention services provided to participants varied greatly – “the ‘standard of prevention’ between and within HIV prevention trials is anything but ‘standard’” (McGrory et al., 2010, p. 24).

Standards of prevention and care⁸ were explored at ten IAVI-affiliated research centres in East and Southern Africa to understand variations, similarities and gaps in services provided, recipients of services, referral systems, and barriers to referral uptake (Ngongo, Priddy et al., 2012). Findings indicated variability in the provision of services. While HIV risk-reduction counselling, male condoms and management of STIs were provided consistently, female

⁸ A review of the care findings is beyond the scope of this study.

condoms, VMMC, and PEP in the case of rape were less consistently provided. Referral systems were established for VMMC and PEP at most research centres but challenges with referral uptake were reported (Ngongo, Priddy, et al., 2012). Research centres endeavoured to provide a variety of services to non-trial participants but there was concern that this might constitute an undue incentive or make conducting research prohibitively expensive (Ngongo, Priddy, et al., 2012). Based on these findings and consideration of scientific priorities, contextual realities, community expectations, equity and cost-effectiveness, the authors developed a set of required and recommended services to be provided on-site or via referrals (Ngongo, Priddy, et al., 2012). For prevention interventions not widely available, it was recommended that research centres consider either training site staff or identifying organisations in the community that could provide such services. In particular, it was recommended that research centres ensure referral for PEP in cases of rape based on national guidelines or international guidelines where there is no national policy; or provide such services on-site (Ngongo, Priddy, et al., 2012). Some informal evaluation of the quality of referral networks was recommended in terms of the provision of specific services such as VMMC, since referrals were to public healthcare services where formal evaluations were not common practice (Ngongo, Priddy, et al., 2012). In terms of prevention interventions, these authors distinguished between those that are required on-site or through referral and those only recommended (see Table 2).

Table 2.

Recommended and required standard of prevention interventions for IAVI-affiliated clinical research centres

Standard of prevention intervention	On-site provision	Referral
HIV VCT	Required	
Basic social support counselling	Required	
Professional social support counselling		Required
Male condoms	Required	
Female condoms	Recommended	
Syndromic management of STIs	Required	
STI diagnosis	Recommended (if available)	
Information and education on VMMC	Required	
Surgical procedure: VMMC		Required
PEP (occupational exposure)	Required	
PEP (in cases of rape)	Recommended	Required
STI diagnosis and treatment for partners of participants	Recommended	Required

From Table 2, it is clear that the authors have identified different obligations for different prevention interventions and different moral groups, although they have not specified their rationale for such distinctions. For example, male condoms are required while female condoms are only recommended; access to the only female-initiated method approved for use in many settings is not even required through referral. This weak obligation is even superseded by responsibilities to ensure access to STI treatment for participants' partners for whom on-site provision is recommended but at a minimum referral is required. Further, there is no consideration of the use of PEP for all risky sexual exposures.

South African researchers have investigated the uptake of circumcision by male participants in an efficacy trial (Phambili) and found that 17.7% of those eligible underwent the procedure (de Bruyn et al., 2009). The authors argue that an uptake of this magnitude may decrease incidence rates and consequently influence sample size requirements. Factors such as feasibility may play an important role in decision-making about what services to provide to participants and when to add new prevention tools to the standard of prevention.

5.3 Stakeholder perspectives on the standard of prevention

Few empirical studies have investigated the perspectives of research stakeholders on the standard of prevention in HVTs. These are significant yet missing perspectives since ethics guidelines require negotiation with all key stakeholders on the standard of prevention, and different stakeholders may have vastly different opinions on factors to consider when making decisions about what to include in the prevention package (McGrory et al., 2010).

At a consultation on standards of prevention held in Uganda in March 2009, representatives of various (though not all) stakeholder groups presented their perspectives. The South African MCC reported that typically, significant results in two RCTs are required before a product/intervention is approved (McGrory et al., 2010).

DSMBs noted that their obligation is to trial participants and an important consideration for them would be whether withholding a successful intervention from participants is ethical. They are not however responsible for considering if and how their decisions about halting or continuing trials may affect other planned or ongoing studies (McGrory et al., 2010).

From the perspective of RECs, the risk-benefit ratio is an important consideration. With regard to HIV prevention, RECs typically expect that researchers provide trial participants with nationally approved and available prevention methods. Researchers must be explicit about how often the risk-reduction intervention will be provided to participants, the study staff responsible for delivering the service, and the required infrastructure. There is still reportedly some debate among RECs regarding whether a new proven method must be made part of the prevention package if it has not been tested or implemented in the community where the trial is planned (McGrory et al., 2010).

Investigators discussed the tension between their desire to provide participants with a range of interventions and services, including new risk-reduction methods, versus providing a core package of risk-reduction interventions consistently and well (McGrory et al., 2010). While some investigators argued that new efficacious interventions should be provided to participants, others suggested that investigators fulfil multiple roles with limited resources, which may make requirements to add new tools to the prevention package unrealistic. Those of the latter view also argued that given the absence of guidelines for the type of prevention package that must be provided, it would be more feasible to develop a core evidence-based prevention package with enough flexibility to be adapted for different trials and trial contexts (McGrory et al., 2010).

Principal Investigators (PIs) ($n=14$) of phase IIB/III HIV prevention trials were interviewed to identify practices and perspectives regarding the negotiation of standards of prevention in trials (Haire & Jordens, 2013). Findings revealed disparate views of PIs on standards of prevention, and that little consensus on the standard of prevention existed, even among these key decision-makers. In particular, differences in opinion were noted regarding whether the standard of prevention should be the best available anywhere, justified as ethically and epistemologically sound; or whether it should approximate local realities justified on scientific validity grounds. In practice, decisions to add VMMC were made based on variable criteria: some PIs reported that the decision was based on the scientific evidence while others had waited for national guidelines. Respondents appeared more restrained in terms of their views on whether PrEP should be included as part of the standard of prevention. Respondents in this study negotiated complex systems that structured what was and what was not possible in their particular trials, including funding constraints, regulatory systems, ethics guidance,

ethics review processes and requirements, and healthcare systems in the host country (Haire & Jordens, 2013).

From the community perspective, it was observed that several approaches have been utilised for community consultations, some more effective than others. However, the common denominator is that all consultation efforts were employed with the purpose to 'consult' communities whereas more recent ethics guidelines (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) require 'negotiation' with research stakeholders. Concerns have been raised regarding the feasibility of negotiation given apparent power differentials between researchers and CABs (Haire et al., 2013; McGrory et al., 2010; West Slevin et al., 2008). Given the strict timelines within which trials are conducted, there is a need to explore multiple mechanisms for achieving the requirements of consultation and negotiation outlined in ethics guidelines, so that complex and sometimes technical decisions can be made timeously (McGrory et al., 2010). It was also argued that 'while it may not be practical from a substantive or logistic standpoint to consult with all research stakeholders on all issues, it may be more feasible and realistic to outline which organisations or entities among stakeholders are well placed to address different aspects of a trial' (McGrory et al., 2010, p. 22).

A recent qualitative study explored ethical and participatory issues related to the conduct of biomedical HIV prevention trials among marginalised populations in Thailand (Allman et al., 2014). This study considered findings in relation to GPP guidelines (UNAIDS/AVAC, 2011). Suggestions were made to improve ethical and participatory practices related to standards of prevention, informed consent, communication and human rights. Regarding the standard of prevention, respondents reflected on the normativity of ethics, some of whom perceived ethics as 'culturally dependent, embodying elements of morality and enforceability that varied with nation, community and institutional context' (Allman et al., 2014, p. 2), even questioning the applicability of international ethics guidelines to the Thai context. When international ethics guidelines are implemented in different prevention trial contexts, international standards of prevention may supersede local services (raising concerns about unethical standards); in other cases, international standards may be inadequate depending on the study population (Allman et al., 2014). Discrepancies between norms in ethics guidelines and actual practices are possible. For example, while sterile needles for IDUs are considered an important component of the standard of prevention in HIV prevention trials

(UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), some sponsor policies might restrict their provision (Allman et al., 2014; UNAIDS/AVAC, 2011). It was argued that despite international guidance, community expectations of the standard of prevention in the local context might differ from what researchers and trial sponsors were willing to offer based on interpretations of local laws and policies, as well as international donor funding restrictions (Allman et al., 2014, p. 3).

5.4 Stakeholder perspectives on ethics guidelines

The introduction and/or revision of HVT-specific guidelines has been accompanied by some exploration of stakeholder perspectives of guidelines. An assessment of the global implementation of GPP guidelines (UNAIDS/AVAC, 2011) found increases in support and awareness of these guidelines but gaps in practices related to documentation of engagement activities and stakeholder input in trial protocols (Hannah, Warren & Bass, 2012). A quantitative assessment of GPP guideline (UNAIDS/AVAC, 2011) implementation at HIV prevention research clinical centres (Ngongo et al., 2012), found lower support for guidance points on standards of prevention at baseline, but this was found to improve after an evaluation workshop which sought to identify the strengths and limitations of these guidelines.

At two regional workshops to pilot test training curricula developed by WHO, UNAIDS, and the African AIDS Vaccine Programme (AAVP), key stakeholders, including REC members, researchers, advocates, policymakers, research sponsors, government representatives, and regulators exchanged perspectives on the UNAIDS/WHO (2012) guidance document. Stakeholders argued for a procedural approach focused on structured negotiation processes as the best strategy to make complex decisions, including on access to evolving standards of prevention (Hankins et al., 2009).

South African HVT stakeholders (site staff, CABs and RECs) ($n=98$) participated in a quantitative assessment of their perspectives on ethics recommendations (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) on standards of prevention and care (Moorhouse et al., 2014). Respondents rated each of 20 ethics recommendations on prevention ($n=10$) and care ($n=10$), on five dimensions, namely, familiarity, ease of understanding, ease of implementing, perceived protection, and agreement. Ethics recommendations on care and prevention were rated highly overall, with recommendations regarding informed consent rated most highly.

However, in comparison to recommendations on care, standard of prevention recommendations were rated significantly less positively. Actually, five of the lowest scored recommendations were on standards of prevention (Moorhouse et al., 2014). Respondents considered the ethics recommendation that the protocol should outline how stakeholders negotiate adding new methods to the prevention package (UNAIDS/WHO, 2012) as problematic in terms of ‘familiarity with’, ‘ease of implementing’ and ‘perceived protection’ (Moorhouse et al., 2014). The recommendation that new prevention tools should be added to the package as they are validated or approved by relevant authorities (UNAIDS/WHO, 2012) was rated as most problematic in terms of ‘ease of understanding’. The recommendation that new tools should be added to the standard of prevention based on consultation among all research stakeholders (UNAIDS/WHO, 2012) was rated as most problematic on the dimension of ‘agreement with’. Importantly, stakeholders’ perspectives indicated concerns about the implementability of certain guideline recommendations. The authors recommend that standard of prevention norms in ethics guidelines be prioritised for refinement (Moorhouse et al., 2014).

6. Remaining gaps

Previous empirical studies have explored standard of prevention practices and/or perspectives in HIV prevention trials, including in South Africa (Haire & Jordens, 2013; Heise et al., 2008; Moorhouse et al., 2014; Ngongo, Priddy, et al., 2012).

The empirical data gathered in the GCM mapping study and accompanying abbreviated study (Heise et al., 2008; McGrory et al., 2010) documented practices at sites, and explored (somewhat) the extent to which actual practices corresponded with ethical norms. While this research acknowledged the value of data for ethics guidelines (cf. Heise et al., 2008), recommendations aimed to bring practices closer to ethical ideals rather than to critically reflect on both practices and norms in ethics guidelines.

The exploration of standards of prevention (Ngongo, Priddy, et al., 2012) documented standard of prevention practices at IAVI-affiliated research centres, and used this data to develop a ‘standardised’ prevention package. This study did not aim to compare practices with norms in ethics guidance.

Haire (2013) conducted empirical research with PIs to explore standard of prevention negotiation practices and perspectives. This study did not aim to document standard of prevention services provided in those trials nor to systematically compare practices, perspectives and complexities with related norms in ethics guidelines. Based on study findings, it was recommended that further empirical research be undertaken on standard of prevention practices and perspectives, in order to inform deliberations about whether, or how, to incorporate newly validated prevention interventions (Haire et al., 2013).

Moorhouse et al. (2014) responded to a gap in the literature regarding perceptions of standard of prevention guidance, and in light of findings of this quantitative assessment, recommended that further qualitative research be undertaken to explore in-depth, stakeholder reservations about implementing ethics recommendations.

To date, there has been no systematic empirical assessment of actual practices at South African HVT sites. There has also been limited empirical investigation of how stakeholders in HVTs make decisions on what services to provide or what they perceive to be the challenges in making these complex decisions (Essack, Slack, et al., 2010). Further, there is little information about how individual trial networks and trial sites address questions on the standard of prevention (cf. Macklin, 2008) nor on whether norms in ethics guidelines are implementable in practice (Macklin, 2010). As such, it has been recommended that the prevention services offered to HVT participants and decision-making practices should be assessed (Essack, Slack, et al., 2010). Further, such research should explore whether practices at sites correspond with norms in ethics guidelines (Essack, Slack, et al., 2010; Macklin, 2010) and whether ethics guidelines provide any direction on the dilemmas faced by researchers (Essack, Slack, et al., 2010).

To address these gaps, this research aimed to 1) identify standard of prevention norms in guidelines (Chapter 3) and 2) gather data about standard of prevention practices and perspectives in South African HVTs (Chapters 7-9). It aimed to collect data that would inform the ethical debate about whether a high standard of prevention is feasible in practice (HPTN, 2009; Macklin, 2009), especially in resource-constrained contexts (Macklin, 2010). It aimed to explore the challenges experienced regarding standards of prevention by HVT stakeholders and whether ethics guidance provides adequate direction regarding these concerns. Further, this study examined perspectives on selected standard of prevention norms

in ethics guidelines (Chapter 10). Overall, this study aimed to generate knowledge that might strengthen site practices, inform revisions of normative guidance and better engage affected stakeholders.

Part 3 (Chapters 6-11) of this thesis focuses on the empirical study. The following chapter details the research methodology and outlines the research questions and aims. It justifies the use of empirical approaches to bioethics, considers the philosophical underpinnings of the study, and describes the data collection and analyses strategies. Ethical considerations related to the present study are also discussed.

CHAPTER 6

METHODOLOGY

This chapter describes the research questions and aims of the study. It begins by situating this study within the ‘empirical turn’ in bioethics (Borry, Schotsman & Dierickx, 2005), followed by a description of the research design, methodology and the philosophical underpinnings of this study. The sampling, data collection and data analysis procedures are presented and the rationale for adopting particular approaches explained. Considerations regarding the quality of data and ethics are also discussed (see Table 3 for an overview of the research methodology and process).

1. Research aims and questions

This study was guided by three primary research questions: (1) To what extent do standard of prevention decision-making and implementation practices (current and evolving) resonate with recommendations in ethics guidelines? (2) To what extent do ethics guidelines address the concerns of key stakeholders about standards of prevention? (3) What are the perspectives of HVT stakeholders on evolving standards of prevention and selected standard of prevention norms in ethics guidelines?

This study specifically aimed to:

1. Critically review HVT-specific ethics guidelines to identify stakeholders’ standard of prevention responsibilities in HVTs.
2. Review HVT site documents (e.g., protocols, standard operating procedures, meeting minutes, consultation reports) in order to identify standard of prevention practices at sites.
3. Explore reported standard of prevention decision-making and implementation practices, perspectives and challenges in HVTs (current and evolving).
4. Explore stakeholder perspectives on selected standard of prevention recommendations in ethics guidelines.
5. Explore a) correspondence between ethics guideline recommendations and reported practices; and b) whether ethics guidelines anticipate empirically identified concerns.
6. Make recommendations for strengthened practices and improved ethics guidance on standards of prevention (cf. Kon, 2009a).

Table 3.

Overview of the research methodology and process

EMPIRICAL APPROACHES TO BIOETHICS	
PARADIGMATIC ASSUMPTIONS	
Paradigm	Critical realism (ontology) Interpretive/discursive (epistemology)
Methodology	Qualitative
RESEARCH DESIGN	
Type of study	Descriptive, exploratory and applied
Sampling strategies	Purposive and snowball sampling
DATA SOURCES AND DATA PROCESSING	
Data sources	Desk review of site documents Semi-structured interviews with key stakeholders
Data processing	Verbatim transcription including laughter, speech repetitions and emphases
DATA ANALYSIS	
	Hybrid inductive-deductive approach (Fereday & Muir-Cochrane, 2006) Critical thematic analysis (Braun & Clarke, 2006)
DATA QUALITY	
	Credibility, transferability, dependability and confirmability
ETHICAL CONSIDERATIONS	
	As per Emanuel et al. (2004) framework for conducting research in developing country contexts

2. Empirical approaches to bioethics

Methodological approaches to bioethics have, over recent decades, taken an ‘empirical turn’ from predominantly normative philosophical analyses to the increasing use of empirical research methods (Borry et al., 2005)⁹, called ‘empirical bioethics’ or ‘evidence-based ethics’ (Ashcroft, 2003; Borry et al., 2005). This empirical turn has been accompanied by increasing interest in the relationship between bioethics and social sciences, evinced by dedicated special issues in journals. For example, Contributions of Psychological Science to Empirical Bioethics (*American Journal of Bioethics Primary Research*, 2013); Bioethics and Empirical Research (*Healthcare Analysis*, 2003); and The View from Here: Bioethics and the Social Sciences (*Sociology of Health and Illness*, 2006), among others. The *Journal of Empirical Research on Human Research Ethics* is exclusively dedicated to empirical research on issues of research ethics. Further, the Wellcome Trust Biomedical Ethics Programme was launched in 1997 with the aim of fostering an approach in bioethics that combined normative

⁹ It is beyond the scope of this thesis to fully consider the rationale for the increasing use of empirical research in bioethics. Readers are referred to Haimes, E. (2002). What Can the Social Sciences Contribute to the Study of Ethics? Theoretical, Empirical and Substantive Considerations. *Bioethics*, 16(2), 896113.

philosophical inquiry with social science methodologies (Draper & Ives, 2007). The empirical turn was principally instigated by the increasing dissatisfaction with normative bioethics, demonstrated by the 'social science critique' (Hedgecoe, 2004) which criticised bioethics as being speculative given its theoretical basis, too broad and abstract, and as failing to take into account everyday realities.

Empirical approaches to bioethics acknowledge that empirical data can influence normative bioethics questions and this issue has received considerable attention in the literature (e.g., Borry et al., 2005; de Vries, Turner, Orfali, & Bosk, 2006; Draper & Ives, 2007; Goldenberg, 2005; Kon, 2009a; Leget, Borry & de Vries, 2009; Miller, 2002; Miller, 2013; Smajdor, Ives, Baldock & Langlois, 2008; Sugarman, 2004). There has been intense debate between bioethicists using classical philosophical inquiry versus those conducting empirical studies on bioethics issues (Kon, 2009a) regarding how empirical research conducted in the social sciences can contribute to bioethics (Frith, 2012). Research in the social sciences is concerned with how the world *is* (or is perceived to be) and the analysis of such perceptions and experiences, while bioethics is concerned with how the world *ought* to be (Draper & Ives, 2007). Some authors argue that 'an evidence-based approach is incompatible with bioethics' normative mandate' (Goldenberg, 2005, p. 2) while others contend that empirical data and philosophical inquiry are complementary, and that empirical research can significantly facilitate the refinement of ethical norms (Kon, 2009b; Carter, 2009) by revealing ethical problems experienced in practice (Draper & Ives, 2007; Kon, 2009a; Essack, Koen, et al., 2010) or by enabling the development of contextualised and responsive ethical recommendations (Carter, 2009; Kon, 2009a).

2.1 Types of empirical studies in bioethics

Empirical research in bioethics can be categorised in three (non-mutually exclusive) categories, social science *for* bioethics, social science *of* bioethics and social science *in* bioethics (Draper & Ives, 2007). In *social science for bioethics*, empirical methods are used to substantiate existing theory or identify novel ethical issues that require resolution through normative analyses (Draper & Ives, 2007).

In the *social science of bioethics*, "bioethical debate, the way in which bioethical discourses interact with people and institutions, and the way in which bioethical discourses are acted out, are themselves subject to sociological analysis" (Draper & Ives, 2007, p. 322). This category

studies bioethics as a social phenomenon rather than an abstract philosophical discipline (Frith, 2008). Studies that consider the application of ethical theory in practice, and how scientists perceive ethical issues arising from their research would fall into this category. A social science of bioethics has proved valuable for studies on the factors that influence and moderate ethical decision-making in practice (Frith, 2008).

These two categorisations maintain clear delineations between social sciences and bioethics.

Social science in bioethics aims to dissolve the boundary between empirical data and philosophical inquiry and develop a more bottom-up approach where the development of ethical theory is informed by empirical data, rather than removed from it – ethical theory is –informed directly by the values, experiences, and perspectives of real people – and not solely by the philosopher in his ivory tower – (Draper & Ives, 2007, p. 326). Studies in this category are designed and conducted to document and identify specific responses (e.g., perspectives, issues, practices) which themselves will inform specific ethical debate (Draper & Ives, 2007).

Some studies may seek to address issues at more than one level, and since categories are not mutually exclusive (Frith, 2008), the present study could be argued to incorporate elements of all three approaches to empirical research in bioethics. It incorporates some elements of a social science *for* bioethics in that it seeks to identify standard of prevention complexities experienced by stakeholders. Through exploring their perspectives on key standard of prevention issues, this research may also identify –nuances– to existing ethical complexities. It also incorporates some elements of a social science *of* bioethics in its exploration of how standard of prevention decisions are made in practice and the assessment of correspondence between norms in ethics guidelines and stakeholder practices. The thesis also has elements of a social science *in* bioethics in that it aims to examine standard of prevention practices (empirical data) in relation to norms, and make recommendations for strengthened practices and refinements to ethics guidelines. Further, this research seeks to identify standard of prevention practices and perspectives to inform further normative analyses of this topic.

An alternative framework for classifying empirical research in bioethics is identified by Kon (2009a). Kon (2009a) distinguishes between four hierarchical levels of empirical research

that inform bioethics, and the aims of this study align with some of the categories defined by Kon (2009a).

Lay of the land research is the first level of inquiry. It aims to document current practices, opinions and beliefs (Kon, 2009a). Generally, lay of the land research is descriptive and explanatory in nature and may be driven by predefined assumptions (Kon, 2009a).

Documenting standard of prevention practices and complexities at HVT sites (Aim 3) could be considered as falling in this category. Data at this level can be useful for the development of policies, can facilitate provider decision-making and help inform future research (Kon, 2009a).

Ideal versus Reality studies explore the extent to which actual practices reflect ethical ideals (Kon, 2009a). However, the premise is that the ethical ideal is uncontested, so this level aims to effect changes to the current practices that deviate from ethical norms. The present study, in its assessment of correspondence between actual practices and norms in ethics guidelines (Aim 5), can also be categorised at this level with the exception that, this study did not uncritically accept ethics norms as uncontested. In this way, this study makes recommendations (Aim 6) that could helpfully inform levels three and four below.

The third level of empirical research, *Improving Care*, considers how to best align actual practices with ethical ideals, in other words, to address complexities identified at the *Ideal versus Reality* level (Kon, 2009a). Studies at this level typically design and evaluate methods or interventions to help clinicians improve care practices so that they are better aligned with ethical norms.

Finally, at the highest level of the hierarchy are empirical studies on *Changing Ethical Norms* (Kon, 2009a). Through a review and bioethical analysis of multiple empirical studies, changes are recommended to ethical norms (Kon, 2009a). However, such studies do not indicate that norms hinge on public opinion but that empirical research helps develop ðrealistic ethical constructsö (Kon, 2009a, p. 62).

This hierarchical framework (Kon, 2009a) however, is not without critics (e.g., Emerson, Upshur & Daar, 2009; Sugarman, Kass & Faden, 2009). In considering that empirical data indicate what -isö this framework is accused of inadequately considering the limitations of

empirical research (e.g., validity, reliability, generalisability) and failing to acknowledge that empirical research cannot produce a mirror of reality, but rather theoretically informed arguments of a particular version of reality (Carter, 2009; Dunn & Ives, 2009). In this study, respondent reports on standard of prevention practices are not seen as direct reflections of standard of prevention practices at sites, but as different perspectives/accounts of the various ways in which the social world (reality) is experienced (Snape & Spencer, 2013). The quality of the data is also explored, as are study limitations. Secondly, while normative theories offer frameworks for interpretation of empirical data, it is argued that they can also be produced in empirical studies (Carter, 2009). Finally, this framework has been criticised for failing to consider research in developing country contexts (Emerson et al., 2009). In such contexts, empirical research at lower levels of Konø (2009a) hierarchy may be able to promote normative changes reserved only for higher levels, in a way that considers ethical reform from the bottom up (Emerson et al., 2009). This study considers this criticism, and provides recommendations for strengthened practices and improved guidance (see Chapter 12).

3. Methodological approach

This thesis interconnects several disciplines in its use of empirical social science methods to explore an ethical issue in a clinical research context.

The present study was conceptualised within the critical realist ontology (the nature of reality). Critical realists assume that data can provide information on an external reality, although unlike realists, it is not understood as a mirror image of reality (Snape & Spencer, 2013). In other words, it is assumed that an external reality exists independently of an individual's subjective understanding but that it is only accessible through socially constructed meanings, that is, via respondents' interpretations (Snape & Spencer, 2013). In this way, language is used to construct social realities (Sims-Schouten, Riley & Willig, 2007). Therefore, respondents' own interpretations of the relevant research issues are important, with different perspectives indicating different vantage points, reflective of the various ways in which the social world (reality) is experienced (Snape & Spencer, 2013). The assumption that an external reality exists however, does not entail that 'absolute knowledge of the way it works is possible' (Scott, 2005, p. 634). Therefore, interview data cannot be taken as literal representations of an external reality; but they do provide important perspectives about a phenomenon that exists outside the interview context (standards of prevention in HVTs). Accordingly, it is argued that 'we need not hear interview responses

simply as true or false reports on reality. Instead, we can treat such responses as displays of perspectives of moral formsö (Silverman, 1993, p. 107).

Epistemologically, this study adopted the perspective that öthe way of knowing reality is by exploring the experiences of othersö (Nieuwenhuis, 2010, p. 55). As follows, this study incorporated the two quintessential interpretive principles of understanding in context (*verstehen*) and the positioning of the researcher as the primary instrument/medium in data collection and analysis (Merriam, 2002). Although the research was predominantly guided by interpretive principles, where relevant, the researcher adopted a more critical (discursive) approach towards interpreting and understanding respondentsøaccounts. In marrying these approaches, the research position varied between first-person and third-person perspectives ó in understanding stakeholdersøstandard of prevention practices, perspectives and challenges, the researcher primarily adopted an empathic epistemology; however, by implementing Ricouerø (1973) concept of distanciation, the analysis was able to offer a more critical interpretation, where relevant. Discourse analysis centres on the way knowledge is produced through talk, (e.g., ethical discourse, medical discourse) or through implicit theories so as to make sense of social action (e.g., culture, power, gender relations). Discourse analysis may also focus on the details and dynamics of the interaction, including, in terms of respondentsø use of representations and rhetorical devices (Silverman, 2005).

Such dual approaches have been previously applied in research on masculinity (Davies & Eagle, 2007; 2010), women and motherhood (Sims-Schouten et al., 2007) and volunteering in child abuse services (Alexander, 2011). The resultant critical thematic analysis (Braun & Clarke, 2006) appeared to consolidate these theoretical orientations in a way that accommodated the perspectives and experiences of respondents as well as the discursive contexts in which they attach their meaning systems.

4. Research design

This study, which focused on standards of prevention in HVTs, was embedded in a larger project on HIV care and prevention in South African HVTs. The related studies qualitatively examined applicable ethics guidance and the provision of ancillary care services in HVTs (Slack et al., 2014); and quantitatively explored stakeholder perspectives on care and prevention norms in applicable ethics guidelines (Moorhouse et al., 2014).

This study was descriptive, applied and exploratory. Firstly, a descriptive approach was selected because a key aim of this study was to describe stakeholder practices regarding the standard of prevention in HVTs.

Secondly, a review of the literature revealed a paucity of empirical studies on standards of prevention in HVTs generally, and in South Africa, especially in relation to norms in relevant ethics guidelines. As such, an exploratory approach was adopted since exploratory research is useful when there is limited knowledge about a particular topic (Durrheim, 2006).

Thirdly, given its pragmatic focus on actual practices in HVTs and its assessment of correspondence between practices and ethics guidelines, this study had an applied component. Further, it was anticipated that findings from this study would contribute towards improving decision-making and implementation practices in HVTs as well as strengthening standard of prevention recommendations in ethics guidelines. This is in line with one of the primary aims of applied research which is to collect and generate data that can improve understanding of real-world problems (Guest, Namey & Mitchell, 2012) and its potential for generating actionable outcomes (Ritchie & Spencer, 2002).

Given the exploratory and descriptive nature of the study, a qualitative research approach was selected (Mouton & Marais, 1991). Qualitative research is generally inductive and flexible in nature. As defined by Denzin and Lincoln (1994, p. 2), "qualitative research is multimethod in focus, involving an interpretive, naturalistic approach to its subject matter. This means that qualitative researchers study things in their natural settings, attempting to make sense of, or interpret phenomena in terms of the meanings people bring to them."

A qualitative methodology is well suited for descriptive and exploratory research because it permits an open-ended and flexible approach, which allows for further probing and enables interviewees to respond in their own words, rather than to a set of predetermined categories (Mack, Woodsong, MacQueen, Guest & Namey, 2005). An open-ended approach also enables responses that are both meaningful and culturally relevant to the respondent, largely unanticipated by the researcher, and rich and explanatory in nature (Mack et al., 2005). In addition to the "what", it allows for exploration of the "why", the "who", and the "how" (Mack et al., 2005; Sandelowski, 2000).

Furthermore, qualitative research is described as well suited to exploring the ethical issues experienced in practice (Sanker & Jones, 2008). Qualitative research can help identify how bioethics is achieved in practice by illuminating the practical ethical work being undertaken through the day-to-day choices, priorities, decisions, and actions taken by [people] (Spallone, 1999, p. 21). By producing rich descriptions of actual practice, qualitative research may reveal novel ethical concerns (Essack, Koen, et al., 2010; Sankar & Jones, 2008). Furthermore, qualitative research takes people's subjective experiences seriously, and in so doing, can improve perceptions of the credibility of HVTs (Essack, Koen, et al., 2010).

4.1 Sampling

Stakeholder groups, namely HVT site-staff (e.g., clinicians, counsellors, PIs), CAB members, REC members and research network representatives were selected due to their involvement in the implementation, review, and coordination of HVTs. Respondents¹⁰ from key stakeholder groups were purposively sampled (Mason, 2002). This sampling strategy is based on careful selection of cases that are typical of the population being studied and is often used to create small, relevant samples in qualitative research (Terre Blanche, Durrheim & Painter, 2006, p. 563). Some respondents were also selected using snowball sampling techniques (Biernacki & Waldorf, 1981), for example where respondents made suggestions of other suitable interviewees.

At the time this research was undertaken, there were five trial sites conducting prophylactic HVTs in South Africa, and two trials were ongoing. This study explored standards of prevention practices for both trials (phase I and phase IIB) at all five sites. The phase I trial, conducted at two sites, investigated the safety of a vaccine in HIV-uninfected participants at low risk for HIV. The phase IIB trial, conducted at five sites, investigated the safety and efficacy of a vaccine in HIV-uninfected participants at high risk for HIV.

Forty-four interviews (prevention-specific, care-specific or combined) were conducted with 36 respondents. Prevention-specific interviews were conducted with 14 respondents and general interviews were conducted with 15 respondents. Additional relevant data came from

¹⁰ The terms interviewee and respondent indicate those who participated in interviews for the present study, while the term participant is used for individuals who participate in HVTs.

15 care-specific interviews with 14 respondents, where prevention-related references were made. Because this research was qualitative, pre-defined sample size calculations were not warranted. Rather, sample size was determined by respondents' willingness to participate. Therefore, the number of respondents in each stakeholder group and across different sites varied. Breakdowns of the sample by stakeholder group/interview type and across sites are captured in the Tables 4 and 5 below.

Table 4.

Number of interviews by stakeholder group

Interview type	RECs	CABs	Site Staff	Network	Total
General	8	6	1	-	15
Prevention-specific	-	-	12	2	14
Care-specific	-	-	12	3	15
Total	8	6	25	5	44

Table 5.

Number of interviews by site

Stakeholder	Site 1	Site 2	Site 3	Site 4	Site 5
CAB: General	1	1	1	1	2
Site Staff: Prevention	3	4	1	1	3
Site staff: Combined	-	1	-	-	-
Site Staff: Care	2	2	2	4	2
Total	6	7	4	4	7

Table 6.

Characteristics of the study sample

Role	Male	Female
Principal Investigators	1	5
Site leadership (Directors, Sub-investigators, Research Managers, Study Coordinators)	2	5
Study clinicians	0	1
Community Liaison Officers	1	1
Counsellors	0	2
Network leadership	2	2
CAB members	2	4
REC members (including 4 REC chairs)	7	1

4.2 Data collection strategy

The empirical component of this study explored standard of prevention practices in two trials using primary sources (semi-structured interviews with HVT stakeholders) and secondary sources (review of documents, e.g., protocols, ICFs, standard operating procedures [SOPs]).

A letter requesting site documents and outlining the safeguards for trial sites was sent to PIs at all sites (Appendix 2), who granted permission for the release of site documents.

To formally introduce the study to all sites, identify concerns, and collaboratively determine the most appropriate methods for inviting potential respondents to participate in interviews, sensitising visits were undertaken to all sites (Appendix 3). REC chairs were contacted by email, and their permission sought to contact REC members for an interview. Similarly, a network representative was contacted to determine the most suitable approach for inviting network representatives for interviews. Through this initial outreach, a list of potential respondents was developed.

An information sheet on the study was emailed to all potential respondents, along with an invitation to participate (Appendix 4). Some CAB members did not have access to email, and were contacted telephonically, informed of the study, and invited to participate in an interview.

4.2.1 Semi-structured interviews

This study used a combination of face-to-face and telephone interviews to collect data. The sample was geographically diverse (Opdenakker, 2006), and so telephone interviews provided a useful method to minimise the cost of travel and to access participants outside of South Africa (at the research network). Except for the loss of ability to access social cues (e.g., body language), telephone interviews may provide information quite comparable to in-person interviews (Sturges & Hanrahan, 2004, p. 116).

Interviews were semi-structured, broadly guided by key questions and offered an adaptable and reliable means to gather the kind of data needed to conduct empirical bioethics research (Sankar & Jones, 2008, p. 117). Where relevant to the research questions, additional questions (probes) were used to get respondents to elaborate on particular issues. Semi-structured interviews are often used in qualitative research and serve as a guide that can be

adapted to interviewees and circumstances (Babbie & Mouton, 2001). Semi-structured interviews provide an intermediary between the need to collect similar kinds of information from all respondents while allowing each respondent to express their unique perspectives and experiences (Sankar & Jones, 2008).

Site-staff participated in prevention-specific interviews (Appendix 5) while all other stakeholder groups participated in general interviews (Appendix 6). The prevention-specific interview schedule was developed to explore HIV prevention decision-making and implementation practices, perspectives on ethics guidelines, and challenges and successes in conducting HVTs. The general semi-structured interview comprised an exploration of interviewees' perceptions of general issues regarding HIV prevention practices, their perspectives on ethics guidelines, and challenges and successes. The interview guides evolved over the duration of the study as findings of new prevention interventions became available and based on important issues identified in earlier interviews. Interview guides were also tailored to specific stakeholder groups.

Respondents provided their individual informed consent to participate in interviews and for the audio recording of interviews (Appendix 4). Typically, interviews lasted between 45-60 minutes.

The desk review of documents occurred between July 2009 and August 2012, and interviews were conducted between August 2010 and August 2012.

4.3 Data processing and analysis

Given time constraints, the present researcher transcribed a sample of interviews but the majority were outsourced to a service-provider, who was guided by transcript conventions. Interviews were transcribed verbatim to capture pauses, speech repetitions and overlapping talk (Appendix 7).

Standard of prevention practices in documents and interviews were coded using descriptive methodologies. A descriptive analysis (Sandelowski, 2000) was undertaken with the aim of describing *which* HIV prevention interventions were provided, to *whom*, *how* these services were accessed, *who* covered the cost of providing these services, *why* HIV prevention

interventions were provided and *how* decisions were made. The analysis was descriptive because it was devoid of a theoretical framework (Sandelowski, 2000).

Text was also coded using a critical thematic analysis of the data (Braun & Clarke, 2006). Thematic analysis is well suited to revealing the specific way in which individuals or groups conceptualise the phenomenon under study (Joffe, 2011). It is not intrinsically linked to a particular paradigm and can be accommodated by a range of epistemological approaches (Joffe, 2011), including critical realism (Braun & Clark, 2006) and interpretivism (Terre Blanche, Durrheim & Kelly, 2006). The analysis broadly followed stages of analysis identified by Braun and Clarke (2006) and Terre Blanche et al. (2006), as detailed below. However, the process was iterative rather than occurring in six discrete phases.

4.3.1 Familiarisation and immersion

Prior to this study, the present researcher completed a conceptual review of HIV prevention responsibilities in HVTs (Essack, Slack, et al., 2010), and participated in consultations related to this issue (e.g., Heise et al., 2008; Philpott et al., 2011). Before data collection commenced, relevant literature and ethics guidelines on standards of prevention were reviewed. Therefore, initial ideas about standards of prevention were developed early on, and informed the development of semi-structured interview guides, facilitated probing in interviews, and influenced the subsequent coding and analysis of data.

In and of itself, the process of collecting data allows the researcher to develop initial analytic insights and thoughts (Braun & Clarke, 2006; Terre Blanche et al., 2006). While most of the relevant data came from interviews conducted by the present researcher, some additional relevant data came from interviews conducted by another researcher, illuminating the importance of multiple readings of the text as a first step in analysis.

The process of transcription offers another opportunity to become acquainted with the data (Braun & Clarke, 2006). Since some of the transcription was outsourced, to ensure accuracy, transcripts were checked whilst listening to the digital recording, facilitating the immersion process.

This process of repeated reading of the text, listening to original recordings (Braun & Clarke, 2006) and making annotations, resulted in thorough immersion with the data and enabled preliminary codes/analyses to be developed.

4.3.2 *Generating initial codes*

The preliminary codes, developed through the process of immersion and familiarisation, were systematically applied to the data using a hybrid inductive-deductive approach (Fereday & Muir-Cochrane, 2006). Through this process, new codes were also developed. Although interpretive and exploratory approaches generally employ inductive coding techniques, because this study aimed to explore the extent to which practices corresponded with standard of prevention norms, a flexible hybrid inductive-deductive approach (Fereday & Muir-Cochrane, 2006) was used. The research questions and ethics framework informed an *a-priori* coding template. Text was also inductively coded to identify emerging themes. Some sections of text were assigned multiple codes while some were not coded if they were considered irrelevant to the research question. At this preliminary phase, codes were identified by highlighting text in different colours on printed transcripts. Annotations were made linking codes to ideas raised in the literature and to the normative framework. Preliminary interpretations of the data were also made.

4.3.3 *Identifying themes*

After step two, a long list of codes was generated. In this stage, related codes were clustered and re-clustered as necessary, to form coherent overarching themes (Braun & Clarke, 2006).

According to Boyatzis (1998), themes may be identified at a semantic (explicit) level or at a latent (interpretive) level. This analysis predominantly focused on identifying themes at a semantic or surface level (the what, why, who and how) to facilitate thick description of standard of prevention decision-making and implementation practices. However, even at this level, there was an attempt to interpret themes in relation to previous literature and normative frameworks to explore broader meanings and implications (cf. Braun & Clarke, 2006). This analysis is largely the approach adopted in Chapters 7-10.

In Chapter 11 (Discussion), the analysis is conducted at the latent level to explore the underlying ideas or assumptions that inform stakeholders' reports of complexities with standard of prevention decision-making and implementation. Rather than descriptive, latent

analysis is interpretive (Braun & Clarke, 2006). When thematic analysis is focused at the latent level, it starts to intersect with discourse analysis (Braun & Clarke, 2006), generating a critical thematic analysis. Figure 5 below provides an example of the relationship between subthemes, semantic-level themes and latent-level themes.

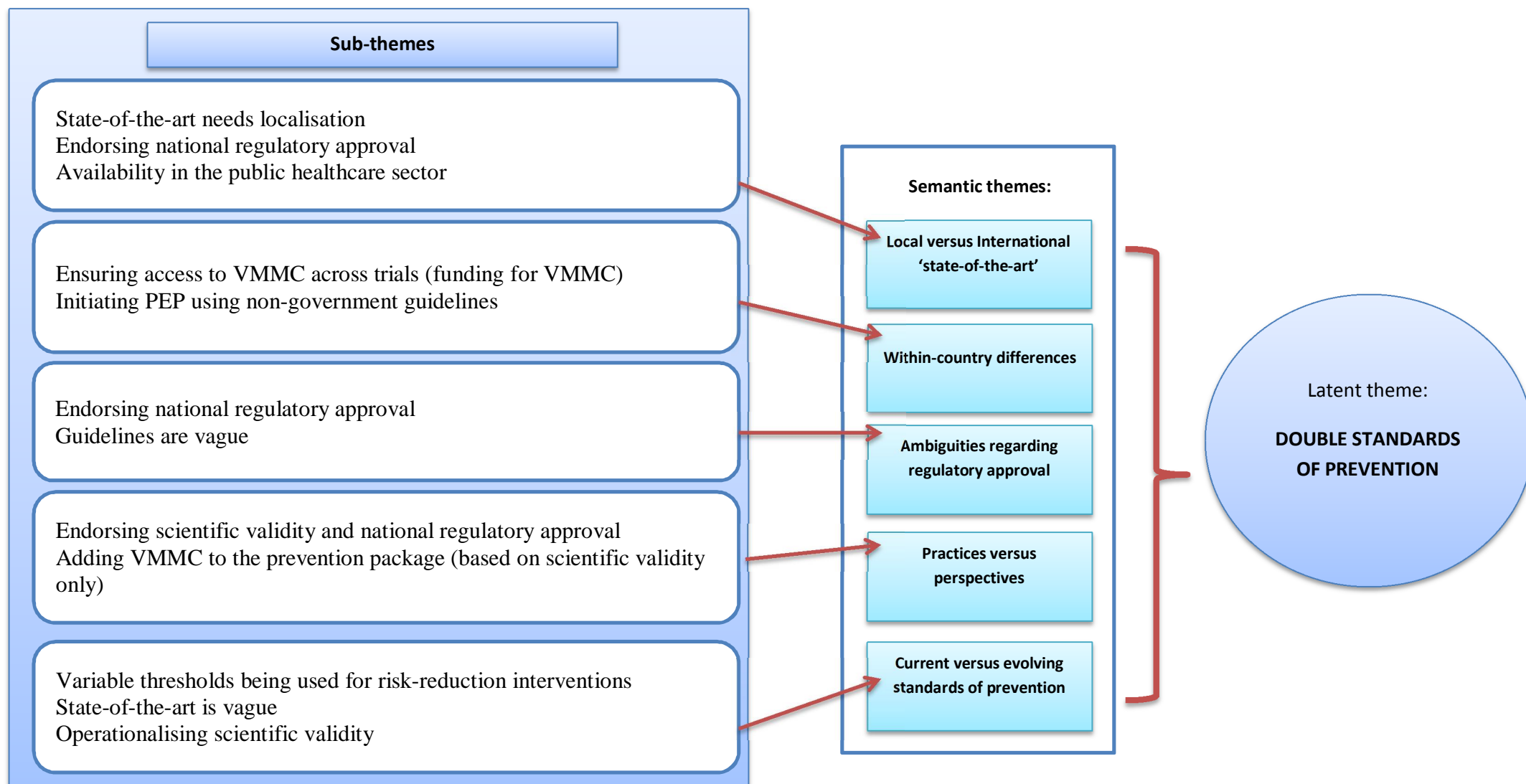


Figure 5: The relationship between sub-themes, semantic themes and latent themes

4.3.4 Reviewing themes

Phase 4 involved refining the preliminary themes developed in phase 3, and occurred in two stages: coded data extracts were examined to identify whether they cohered with the overarching theme. Once this was achieved, the coherence of themes in relation to the data set as a whole was considered (Braun & Clarke, 2006). Themes were also considered in relation to each other, and merged or separated if warranted by significant overlap or differences. Some themes were discarded. Sub-themes (or themes within a theme) were also identified during phases 3 and 4. Once this process was complete, each interview was then coded electronically using QSR NVivo 10 (qualitative data management software). Once all interviews were coded electronically, further amendments were made to the coding framework as necessary (see Appendix 8 for final coding framework).

4.3.5 Defining and naming themes

During this phase of analysis, names of each theme were finalised and definitions were developed (cf. Braun & Clarke, 2006).

4.3.6 Interpretation and writing up

The final phase of analysis involved consolidating themes with the aims and research questions to inform the final interpretations of the data (Terre Blanche et al., 2006). Finally, writing up the findings involved the careful selection of compelling supporting extracts for themes. In some instances, text used in supporting extracts was slightly edited through the deletion of text (indicated by ellipses) in order to improve readability without altering the meaning. The relevance of themes identified in this study was highlighted through linkages to available research, literature and normative frameworks. Further, interpretations were used to formulate emerging answers to the research question and draw conclusions from the data (Braun & Clarke, 2006). The scholarly report of the analysis is consolidated in remaining chapters of this thesis.

5. Ethical considerations

This section details the ethical considerations of this study, according to Emanuel et al. (2004) widely cited (354 Google Scholar citations by August 2014) framework for considering the ethics of research in developing countries.

5.1 Collaborative partnerships

The principle of collaborative partnerships encourages researchers to develop research in collaboration with relevant stakeholders (Emanuel et al., 2004). Prior to the implementation of the study, a national consultation was held with 23 representatives (mainly PIs and CABs) from all sites to inform them about the study and obtain their inputs. Consultation participants made recommendations for improvements to the study and expressed concerns about potential risks to sites (e.g. less developed sites being 'openalised'). Measures to reduce such risks were discussed.

5.2 Social value

The social value of research lies in its ability to address questions that are of value to society or generate knowledge of benefit to participants and/or society (Emanuel et al., 2004; Wassenaar & Mamotte, 2012). In responding to calls in the literature (Essack, Slack, et al., 2010; Haire et al., 2013; Macklin, 2010) to explore standards of prevention in trials, and their correspondence with ethics guidelines, this study hopes to generate knowledge of potential benefit to ethics deliberations on standards of prevention in HVTs. An explicit aim of this study is to identify recommendations for improved practices and guidelines, and, in this way, this study hopes to be of benefit to study respondents.

5.3 Scientific validity

This principle emphasises the importance of scientifically sound research design, sampling strategies, and data collection and analysis processes, since research that is not scientifically valid is not ethical (Emanuel et al., 2004). The measures implemented in this study to enhance rigour, validity and reliability are explained below and summarised in Figure 6.

This study adopted a critical realist ontology, assuming that there is an underlying reality which can be studied but that data provides a representation of that reality that is perspectival, rather than absolute (Scott, 2005). While the concepts of reliability and validity were developed for positivist research, in their broadest conception, they are applicable to qualitative research (Lewis & Ritchie, 2013). Several strategies were used to ensure to reliability and validity in this study.

Rather than validity in the quantitative sense of measuring what the researcher claims to measure, in qualitative research validity is understood in terms of the credibility and

transferability of the data (Lincoln & Guba, 1985). In qualitative research, reliability is less concerned with whether a replicated study would produce similar findings but with the 'trustworthiness' (Glaser & Strauss, 1967), 'consistency' (Hammersley, 1992) or 'dependability' (Lincoln & Guba, 1985) of the data. Efforts to ensure credibility and consistency are detailed below. Issues of transferability (generalisability) and reflexivity are discussed in Chapter 11.

5.3.1 Triangulation

Triangulation is the use of multiple methods to study the same phenomenon or the analysis of the research question from multiple perspectives to enhance the credibility of research (Guion, Diehl & McDonald, 2011). This study employed several strategies of triangulation including data triangulation, methodological triangulation and investigator triangulation.

Data triangulation involves using different sources of information/data (Guion et al., 2011). In this study, document review and semi structured interviews were used as sources of data. Data triangulation can also be considered in terms of categories of time, space, and person (Begley, 1996). In this study, data triangulation of space and person were used. Space triangulation was used by collecting data from multiple HVT trial sites and different RECs (Begley, 1996). In terms of person (stakeholder) triangulation, semi-structured interviews were conducted with various stakeholders involved in HVTs, and within sites, staff with differing responsibilities were sampled, e.g., PIs, clinicians and counsellors. By conducting interviews with multiple representatives of stakeholder groups, this study was able to get different accounts and perspectives on standards of prevention practices. Unit of analysis triangulation (Begley, 1996) entails employing two or more approaches to analysis. This study employed descriptive, interpretive and critical approaches in the analysis of data.

The use of different researchers during the coding process (investigator triangulation) was used to ensure reliability of coding and to enhance the credibility of the research. The coding framework for decision-making was jointly developed with a second independent coder based on a reading of a sample of transcripts, key literature, and ethics guidelines. Where there were discrepancies in coding, these were resolved through reconciliation discussions (Boyatzis, 1998). Codes identified in the initial reading of transcripts were consolidated into a coding framework. The development of the coding framework was iterative. The preliminary coding framework was used to code two additional transcripts, and after reconciliation

discussions, amendments were made as necessary, where some codes were merged and others discarded altogether (see Appendix 8).

The present researcher developed the coding framework for implementation practices and perspectives. To enhance reliability of coding, a portion of interview data (STI treatment) was co-coded by a second researcher and followed the same process of reconciliation discussions to resolve disagreements (Boyatzis, 1998). Similarity in the identification of themes and interpretations of this data were also compared.

In order to ensure the reliability of analysis in qualitative research, it is recommended that researchers present actual data from respondents rather than their own inferences when presenting the final analysis (Silverman, 2005). For this reason, extracts from interviews are used to support interpretations of the data (see Chapters 7-10).

5.3.2 Respondent validation

Respondent validation (member checking) requires that the researcher's account or interpretation of the data is compared to respondents to determine correspondence (Mays & Pope, 2000). Respondent validation is considered valuable for ensuring the credibility of a study's findings (Lincoln & Guba, 1985). The range of feedback to respondents varies and may include sending transcripts or quotes to respondents to verify accuracy, or providing an opportunity for respondents to comment on the interpretations of draft reports (Lacy & Luff, 2012). In the present study, the feedback consultation with stakeholder representatives, including some respondents, could be argued to serve as a strategy for respondent validation. The aim however, was not to verify results, but to feed key findings back to stakeholders (as ethically required), and obtain their inputs/feedback on study conclusions/implications.

5.4 Fair selection of participants

The ethical principle of justice (Beauchamp, 2008) requires that study participants are selected fairly. Participants should be selected from populations to which the research question is relevant (Emanuel et al., 2004; Wassenaar & Mamotte, 2012). As described above, the study sample was purposively selected and included representatives from HVT stakeholders involved in the planning, implementation and oversight of HVTs. The sample was therefore suitable to the research question.

5.5 Favourable risk/benefit ratio

The ethical principles of beneficence and non-maleficence require that potential risks be identified and minimised and benefits maximised (Wassenaar, 2006). It was anticipated that some respondents might experience anxiety about their reported practices being judged as inadequate and potentially resulting in negative consequences for them or their organisation. As such, the research was presented as a collaborative problem-solving endeavour around a shared concern. Prefacing each interview, respondents were informed that their confidentiality would be protected and it was emphasised that respondents could refuse to answer certain questions. Further, to emphasise that this research was undertaken in the spirit of collaboration rather than as an audit, no direct observations of practices were undertaken. Few direct benefits for respondents were expected from this research. However, this research aimed to make recommendations for improvements to practices and ethics guidance.

Respondents who participated in interviews were offered R50 (+/- \$5). It is considered ethical to compensate participants in research for their time and inconvenience (Koen et al., 2008). This payment was not considered to offset risk (Wassenaar & Mamotte, 2012).

5.6 Independent ethics review

This study received ethics approval from five RECs with jurisdiction over trial sites, as follows (approval numbers in parentheses): Biomedical Research Ethics Committee, University of KwaZulu-Natal (BE 241/09); Human Research Ethics Committee (Medical), University of the Witwatersrand (M091140); Medunsa Research Ethics Committee, University of Limpopo (Medunsa Campus) (MREC/P/13/2010: CR); Human Research Ethics Committee, University of Cape Town (REF 476/2009) and The Committee for Research on Human Subjects (Medical), Walter Sisulu University (089/009).

All respondents were informed of the ethics review process and were provided with the contact details of the Biomedical Research Ethics Committee (UKZN), should they have any questions pertaining to ethical issues in the study (Appendix 4).

5.7 Informed consent

Autonomy and respect for the dignity of persons is operationally expressed in the requirements for informed consent in research (Wassenaar, 2006). Individual informed

consent was obtained from all respondents for both their participation in interviews and the audio recording thereof (Appendix 4).

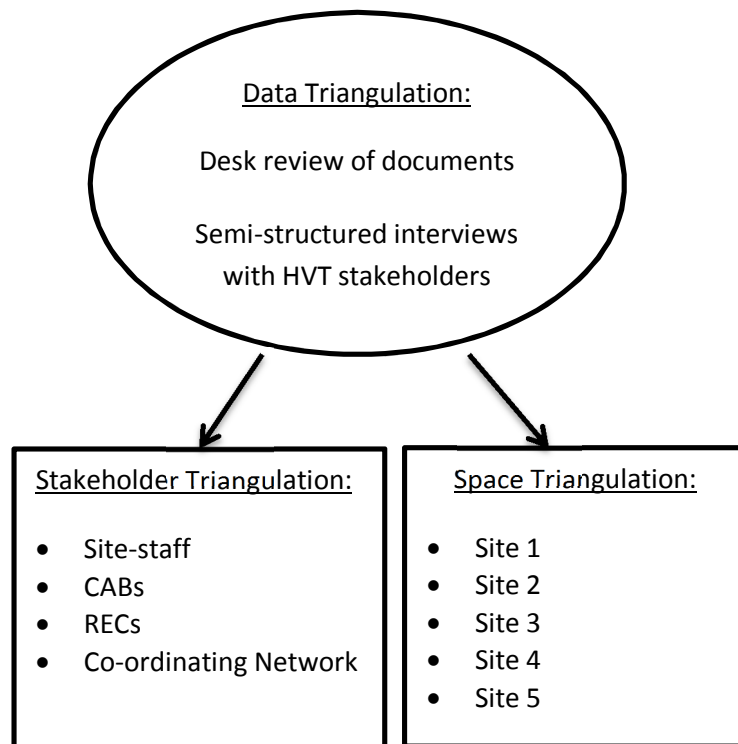
5.8 Ongoing respect for communities and study participants

Participants should be treated with respect during and after a study by ensuring confidentiality, allowing them to withdraw at any time and informing them of study findings (Emanuel et al., 2004; Wassenaar & Mamotte, 2012). In terms of confidentiality, each interview respondent was assigned a code that was recorded on their interview transcript. Records of respondent and organisational identifiers were stored separately from the data. Identification of respondents and their organisations was omitted from public reports. Site data was aggregated to form a national picture. However, since this study sample was relatively small, in some cases individual responses may be identifiable through the use of rich text extracts to support interpretations. This limit to confidentiality was outlined to participants in information sheets (Appendix 4) and every effort was made to reduce this risk.

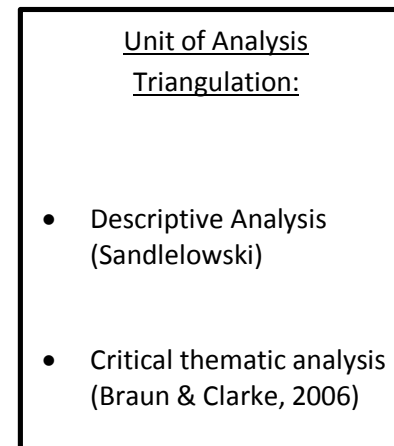
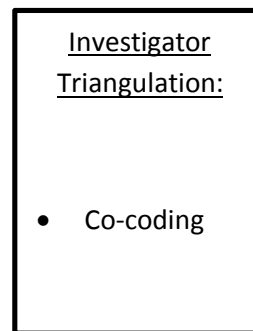
A post-research consultation was held in November 2012, where preliminary results were presented to stakeholders such as sites, CABs and RECs. The aim of this meeting was to provide feedback to stakeholders on the study findings, get their inputs, and stimulate discussion on the implications for practices and ethics guidelines. A manuscript on standard of prevention practices at sites was published (Essack, 2014), and circulated to all respondents who participated in interviews.

MEASURES TO ENHANCE SCIENTIFIC VALIDITY

DATA COLLECTION PHASE



DATA ANALYSIS PHASE



WRITE-UP PHASE

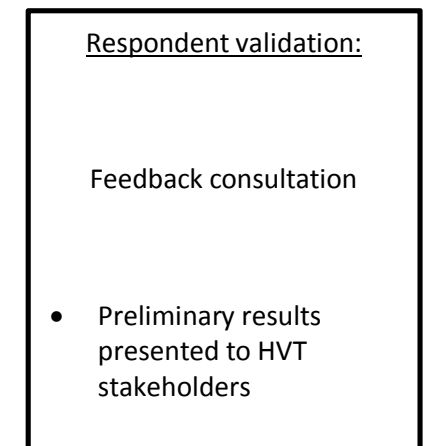


Figure 6: Ensuring rigour in the design and conduct of the study

6. Summary

This chapter outlined the methodology used for this study. This study is located in the empirical turn in bioethics and uses qualitative empirical research to address debates on standards of prevention in HVTs. Specific study procedures, approaches, data collection methods and instruments, and data analysis processes were detailed. The next chapters present findings on standard of prevention practices and perspectives in relation to norms in ethics guidelines and relevant literature.

CHAPTER 7

STANDARD OF PREVENTION DECISION-MAKING PRACTICES AND PERSPECTIVES

"In theory, there is no difference between theory and practice. But, in practice, there is" ó
Jan L.A. Van de Snepscheut

This chapter presents empirical data on standard of prevention decision-making practices and perspectives. It begins with stakeholder perspectives on the rationale for providing prevention services to trial participants (*the why*). Standard of prevention decision-making practices and perspectives are then presented according to the various stages at which decisions are made, namely protocol development, protocol review and protocol implementation. For each phase, the analysis considers the stakeholders involved in decision-making (*the whom*), their related practices and perspectives, the decision-making processes that are utilised (*the how*), and the challenges experienced. Given that most standard of prevention decisions do not occur at site level, this chapter only presents comparisons between sites and stakeholder groups, where relevant. Data in this chapter were analysed using critical thematic analysis (Braun & Clarke, 2006) which involved consideration of discursive undertones where relevant. Decision-making practices are compared with relevant HIV prevention recommendations in ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

1. Why provide prevention interventions to trial participants? The rationale

While there is broad consensus that participants must be provided with effective preventive interventions to reduce their risk of acquiring HIV (Rennie & Sugarman, 2010), there is little consensus on the ethical rationale for doing so (Philpott et al., 2011). Several ethical frameworks have been advocated as justifying the provision of a standard of prevention package (see Chapter 5). Respondents in this study were also asked for their perspectives on why access to prevention services should be ensured for participants, as detailed below.

1.1 To keep participants HIV-negative

Some respondents argued that trial participants should be provided with a prevention package because of the obvious need to maintain their HIV-negative status. Since HVTs enrol HIV-negative individuals with the overarching aim to identify an effective vaccine to prevent HIV

infection, keeping trial participants negative was argued to be congruent with this aim.

“...as researchers we need to remind ourselves of the bigger picture. That whilst we’re doing our trials and whether it’s vaccine trials or microbicide trials or whatever, you know at the end of the day we’re wanting to reduce individuals becoming infected so we therefore need to, focus on that at times. It’s important for us to actually send out the prevention messages because that’s the ultimate goal” (Z22, site staff, site 1).

“I think since the criteria is explained that we need an HIV-negative, we need to maintain them being their negative status throughout the trial. I think that’s the commitment that the sites have to make to the participant which make it upon us that we’ll maintain your HIV-negative status” (Z2, site staff, site 1).

“I think it can help them to stay negative. It is important.” (Z19, CAB, site 4).

The old idiom that ‘prevention is better than cure (treatment)’ was also evoked to justify the provision of prevention interventions in trials. It was argued that “...prevention is what you always aim for...the health of the people is the supreme law.” (C17, REC).

1.2 An ethical obligation

Many respondents purported that providing a standard of prevention satisfies an ethical obligation or ‘moral duty’ (Z17) to trial participants:

“I think it’s critical, it’s an ethical obligation of ours. They’re participating in our trials and uhm gosh uhm it’s the right thing to do (laughs). I don’t know what else to say” (Z13, network representative).

“I think it’s our obligation as ethical individuals (laughs), as ethical, um, researchers, to provide access...there are a number of guidelines as to how to conduct research in communities... all of them are very clear about providing the highest level of prevention available... We do these trials which are incredibly expensive, right, it boggles the mind how expensive they are. Uhm if we didn’t provide a level of care, if we were working in an ethics-free environment, we could do a trial in eight people...we’d vaccinate four people, we wouldn’t vaccinate four people, we’d introduce HIV and see what happens...for God’s sake, that would be a quick way to find out, wouldn’t it? But you know, that’s not the way we do things, and still look at ourselves when we get up in the morning” (Z9, network representative).

“...even at a moral level, I then have to move to say... I will put at your disposal the things I know may work in this environment to reduce your risk.” (Z18, site staff, site 5).

1.3 Beneficence/non-maleficence

Some respondents were able to articulate this ethical obligation in relation to ethical principles. Like UNAIDS/WHO (2012) guidelines, beneficence and non-maleficence were

described by one REC respondent as the justification for providing prevention interventions in that researchers are obligated to maximise benefits and minimise foreseeable harms to trial participants ó *“...in HIV prevention trials the foreseeable risk is seroconversion so that researchers have an obligation to access and provide the best available standards of prevention.”* (C19, REC).

However, like ethicists (Philpott & Heise, 2009), not all respondents considered beneficence to ground standard of prevention obligations.

1.4 Reciprocal justice

The rhetoric used by many respondents (owe, sacrifice, reciprocate, thanking, voluntary contribution) resonates with the ethical principle of reciprocal justice. Participants were deemed as deserving a standard of prevention because research relies on their involvement and they voluntarily risk their well-being to contribute to the development of an HIV vaccine, which if effective, would be of great scientific and social value (Lie et al., 2006). For such contributions, researchers and sponsors, and to a more limited extent society, were argued to have a moral duty in protecting the welfare of participants in these trials.

“...it’s the reciprocity principle. And, in this regard, you find that if somebody is willing to risk their life, and put their life on the line in the interests of science, then it’s an ethical requirement that society or science in general, the scientific community, and sponsors, and everybody who’s part of that, you know, the sector that is going to receive the knowledge, that they actually reciprocate. And, they actually end up, obviously compensating them for whatever it is that they need if they do get infected, or they are provided with relevant prevention measures (.) beforehand.” (Z12, REC).

“I mean our lives depend on the study... We all rely on the information or whatever that they give, because eventually the findings that come from the research will be answer to all of us.” (Z1, CAB, site 1).

“...these are participants who are participating voluntarily and you know just because of their passion about wanting to make a contribution to the academic. So the least that we can do is to offer them the best that we can...” (Z22, site staff, site 1).

“(laughs) I think we owe it to them. ... we are begging them, to come and help us improve this knowledge. ((Vaccines)) are going to help the very same community anyway, but at this point, there are no real benefits for them. So, an obligation... with all that they give to us, they give us their bodies, they give us their information, they give us their time. I think this is personally, and I think it is based upon some literature that, we, we owe it to them....that’s the least we can do.” (Z11, site staff, site 2).

“I think because without participants a site will not have research.” (Z20, CAB, site 5).

Reciprocal justice was an implicit rationale for providing a higher standard of prevention to trial participants than those in the local community or the general population:

“...because of the special sacrifice that research participants in HIV prevention trials are making for the community and for the future of the population that they do, I don’t think there’s any special worry that they might be receiving a higher standard of prevention than people in the community.” (C19, REC).

Obligations to non-trial participants are discussed in chapter 9 on standard of prevention implementation practices and perspectives.

1.5 Therapeutic obligation and clinical equipoise

A few respondents argued that the provision of prevention interventions satisfied the investigator’s obligations to act in the best interests of their participants ó akin to clinicians’ obligations to their patients. It was also justified based on the uncertainty of the efficacy of the experimental vaccine in comparison to the existing standard of prevention.

The provision of a prevention package was argued to not only be for the benefit of trial participants but also as servicing the intrinsic needs of clinician-investigators by satisfying their clinical obligation to save lives and by feeding their self-perceptions as òethical researchersö:

“I think probably the most fundamental reason is it fulfils our responsibilities of investigators.” (Z6, site staff, site 2).

“...it’s one of those two things, you know, that, often, push back in ethical, kind of, discussions, is that it feels good, it looks good to provide a great prevention, you know, intervention along with the trial, because it makes you feel like you’re saving people.” (C5, REC).

1.6 Standard of care

Access to prevention options for trial participants was also justified on the grounds that it is scientifically relevant to compare new prevention interventions against currently available prevention interventions. It would be unethical to deny participants’ access to available HIV prevention options as this would mean that participation in HVTs would potentially increase risk of HIV infection.

1.7 To counteract behavioural disinhibition

Although dismissed as a weak rationale by some ethics commentators (see Lie et al., 2006), providing access to prevention interventions in HVTs was also argued to minimise the potential that participants will increase their risk behaviour because of false perceptions that the vaccine is protective.

1.8 To moderate community mistrust of research

Finally, the provision of a standard of prevention was perceived as tempering community mistrust of research. Some respondents reported that given the history of research in apartheid South Africa (Baldwin-Ragaven et al., 2000; Barsdorf & Wassenaar, 2005), community mistrust of research and researchers still prevailed. It was noted that many communities were still suspicious that HIV vaccine research increased participants' risk of acquiring HIV.

"...because the last thing that you want is to have a situation where the community views our research as actually/ because we're doing prevention research it's like therefore especially where you're finding that HIV infection is your endpoint. Now if we do not offer good risk-reduction counselling that can be easily viewed as that we are encouraging women to become infected so we can reach our endpoint and that is definitely not the aim." (Z22, site staff, site 1).

"...most of the questions that are asked by people 'is this research of yours not going to give us more HIV?' So that is where now we have got to explain to say 'the research is trying its utmost to reduce the incidence of HIV, so there is no way that you can get more HIV in the community.'" (Z3, CAB, site 2).

"...at the moment here people are very suspicious and then because of our history. When things come like this they are suspicious – 'they want to take my blood, what is it? What are they going to do with it and all that.' And the suspicion that the vaccine that they are going to use: 'are they not going to infect me with HIV' and so on so, it takes time to win the trust of the community..." (C12, CAB, site 3).

"It's so they don't think that whatever we doing here, we are giving them the diseases. I think it's very critical." (Z8, site staff, site 4).

1.9 Comparison of perspectives on the rationale for providing access to prevention interventions with ethics guidelines

National ethics guidelines (MRC, 2003) require the provision of risk-reduction interventions in trials on the basis that phase III trials will involve some exposure to HIV infection while the GPP guidelines (UNAIDS/AVAC, 2011), like many respondents in this study, merely articulate that providing a standard of prevention to participants is an ethical obligation.

Beneficence and non-maleficence stated as ethical rationales in UNAIDS/WHO (2012) guidelines and by various commentators, were also suggested as rationales by some respondents. The lack of agreement on the ethical rationale supporting the provision of prevention services to participants in trials (McGrory et al., 2010) was also reflected in the variable justifications provided by respondents in this study.

Many of the responses to the question of why prevention services should be provided to trial participants were peppered with laughter. Laughter seemed to serve several purposes in the research interview. Some of the laughter appeared to suggest the perception that the ethical rationale is obvious and that even asking the question was nonsensical, for example *“Mmm, uhm:: what do you mean? I mean for obvious reasons ...”* (Z7, site staff, site 1) and *“...uhm gosh uhm it’s the right thing to do (laughs). I don’t know what else to say”* (Z13, network representative). The perception that the rationale is obvious did not resonate with the fact that there is no consensus on the ethical rationale for providing prevention interventions (McGrory et al., 2010), nor with this data, which identified multiple rationales.

For other respondents, the laughter appeared to ease tension. Given that this question was posed by a researcher affiliated with an ethics unit, for some respondents, it may have generated a moderate degree of anxiety. For example, *“you’re cleverer than me about all the words like beneficence and all the other things”* (Z18, site staff, site 5). Nevertheless, many respondents appropriately articulated their perspectives in a way that closely mapped with positions identified in related ethics guidance.

In addition to the rationales of beneficence/non-maleficence, reciprocal justice, standard of care, behavioural disinhibition, the therapeutic obligation and clinical equipoise (McGrory et al., 2010) mentioned above, respondents identified community mistrust of research as a rationale for providing prevention interventions.

South African trial communities have been particularly sceptical about clinical trials and mistrust of research has been perpetuated by various myths and misconceptions including that researchers infect participants with HIV (Ramjee et al., 2010) and that HIV/AIDS was manufactured to decrease the numbers of the Black population in South Africa to support the return of the apartheid regime to power (Sivelä, 2012). Such myths and misperceptions find fertile ground in a complex history where under apartheid *“black people were targeted as*

research participants due to their obvious vulnerability (Barsdorf & Wassenaar, 2005, p. 1087). Widely publicised and sensationalised media reports that trial participants are used as ‘guinea pigs’ in HIV prevention research (cf. Ramjee et al., 2007) has further fuelled such mistrust of research. Respondents in this study argued that the provision of a prevention package to participants would help defuse such mistrust and that active efforts to take care of trial participants would engender less scepticism in future trials. GPP guidelines (UNAIDS/AVAC, 2011) acknowledge that efforts to reduce risk of HIV acquisition among trial participants is of great concern to community stakeholders and that negotiation with these stakeholders about the prevention package is likely to impact on community perceptions of the trial.

2. Protocol development practices and perspectives

For every HIV prevention trial, deliberations must occur regarding the standard of prevention to be provided to participants. Accordingly, standards of prevention are an integral component of the study design (Tarantola et al., 2007). Deliberations about the standard of prevention are both ethically and scientifically relevant: the provision of a standard of prevention is ethically mandated (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) and has critical scientific implications for trial design (Padian et al., 2010). Different approaches to standard of prevention discussions were described in interviews, including consultations between the sponsor, network and investigators as well as iterative, informal dialogue among various research stakeholders.

Standard of prevention deliberations primarily occurred during the protocol development process:

“I think probably the main stakeholder, certainly in that particular clinical trial [the phase IIB trial], and I would say clinical trials in general, is the protocol committee. ... And, I think really, the main decisions around what will be in, and what won’t be in ((the prevention package)), is at that level.” (Z18, site staff, site 5).

The protocol committee was represented as the leading decision-making body in terms of establishing the standard of prevention for most trials.

For each trial, a draft study protocol was circulated to members of the protocol committee for review, three weeks preceding a one and a half day face-to-face meeting. The protocol

development meeting was described by a network representative as intensive, methodical and structured:

“So, the protocol’s distributed to us about three weeks before, and we have three weeks to review it. We bring people into a room and it’s a very structured process, so, the first half day...we literally go through the protocol and everybody provides comments. It’s a round-robin, anybody can provide as many comments as they want...everybody is providing input at that point, and then we break into functional groups... our functional group is assigned a couple of different sections, and we are assigned to resolve all the issues that have been raised in that section, and, that’s down in the second half of the first day, and then, at the end of the day, everybody presents back what the resolutions are. That night, staff members from our office complete all the changes in the protocol, and the beginning of the next day, there is a fresh protocol put in front of everyone, with all the changes incorporated, and there’s basically a reading period by which everybody in the room reads through and makes sure that it meets all their requirements, and then, there’s a sign off.” (Z9, network representative).

The above quotation emphasises the collaborative nature of protocol development. It was suggested that all stakeholders represented on the protocol committee were afforded an opportunity to make a meaningful and substantive contribution, including regarding the standard of prevention.

2.1 Stakeholder ‘negotiation’ of the prevention package

GPP guidelines (UNAIDS/AVAC, 2011) affirm that research teams and relevant stakeholders should negotiate the HIV prevention package during protocol development. The protocol committee comprised diverse stakeholders including representatives from the sponsor/funder, the coordinating network, site investigators and the host community.

2.1.1 The sponsor’s role in standard of prevention decision-making

The sponsor was reported to have representation on all protocol committees:

“.. the [sponsor’s] medical officer sits on every protocol team and sits on every protocol safety review team and is sort of intimately involved in the development of the science and in overseeing the operations of the protocol” (C10, network representative).

The intimate involvement of the sponsor in making decisions on all phases of the trial is in line with the sponsor’s role of taking primary responsibility for the initiation, management, and/or financing of a clinical trial. It ensures that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting (Tarantola et al., 2007, p. 4864).

2.1.2 Complexities with sponsor funding policy

Many respondents in this study perceived the sponsor as having supreme decision-making authority. In some circumstances, the sponsor was even portrayed as dictatorial and self-serving by limiting the prevention options that could be made available to trial participants. The rhetorical device of *“othering”* (Johnson et al., 2004) was observed in discussions about the sponsor who was perceived as the stakeholder *“not on the same boat”* (Z5, site staff, site 2) with regard to the welfare of participants (see Chapter 11).

A sentiment shared by some respondents was that the sponsor was solely promoting their own interests:

“...there are the donors driving, funder driving. If the funder said I need 1, 2 and 3, you can’t go beyond that” (Z2, site staff, site 1).

“One of the stakeholders I think it’s the sponsor. Sponsors structure trials according to what they want to study. And beyond that they are not fully committed...So there are some stakeholders who are in the same room but uhm what I’ve noticed is that sponsors are not in the same boat as everybody.” (Z5, site staff, site 2)

“I guess it’s the pharmaceuticals, that’s another industry altogether. We are a site, they are pharmas. They design. They have strict budgets. They say, ‘What we want is this.’ (R: ‘We’ll pay for this.’ Ja¹¹) ‘We’ll pay for this. Anything else. No’. You could negotiate some of those things... but they would not go beyond certain brackets. (laughs). And, I think, sponsors have realised that South Africa is picking up when it comes to clinical trials. They’ve got options. Um, if you put in weird budgets, they will just not take you into their trial and go to [other local sites] (laughs). And they will find a PI there who is willing. PIs must also agree, on certain/ to say, ‘This is what we need, or it’s not happening.’ ... They’re just concerned about their trial, so I think cracking that gap would be another mission. Because they could say, ok, South Africa’s not co-operating when it comes to this, let’s just move it to Zimbabwe, move it to another country.” (C3, site staff, site 2).

*“So for example unless an STI test is mandated by the research we cannot cover the cost of that test. So if it’s, for example, you know a participant retention tool that they can do sort of one-stop shopping for their care...that funding needs to come from elsewhere. We cannot use the money for that. **Not that we wouldn’t like to but we can’t.**”* (C10, network representative, emphasis added)

“So, we were saying to the sponsor I think you’d better pay for the drugs [for STI treatment]...they wouldn’t budge, they wouldn’t. And we were like, ‘Ok find a pharmaceutical company that can sponsor’. But then that was also another red-tape,

¹¹ *Ja* is a colloquial term for yes.

because you can't do it, you have got to do it via the government, and what-not."
(Z11, site staff, site 2).

The above extracts highlight that as the funder and financier of the trial, the sponsor was perceived to command most of the decision-making power. This was characterised by the perception of a relatively non-negotiable sponsor policy and the uneasy acquiescence of other stakeholders with this policy. Still, a few respondents expressed frustration at the funding thresholds imposed by sponsors and the lack of commitment to compromise or with compromise considered a critical aim of negotiation. There was some concern expressed that sponsor policies were intractable and that it was difficult *"to change their [sponsor's] mind-set"* (C17, REC). Sponsor policy dictated for example, that federal funds could not be used to purchase drugs or support care services that are not required for scientific validity or participant safety (Philpott et al., 2010).

While concerns expressed by respondents related primarily to sponsor policy not to fund non-research activities (also described in chapter 9), one respondent was concerned about sponsor decisions to utilise particular guidelines that may not necessarily be helpful:

"Like I was mentioning before, I found the CDC guidelines...to not be particularly helpful which is a little disappointing because that's a requirement that we use the CDC guidelines" (Z13, network representative).

Given sponsor policy, there was an obvious chasm between what sponsors were willing to provide and what ethics guidelines prescribe for trial participants. This gap was bridged via complex arrangements between other key stakeholders as described below.

2.1.3 The investigator's role in standard of prevention decision-making

Investigators were represented on the protocol committee and played a pivotal role in determining the standard of prevention, particularly for the phase IIB trial. It was described that protocol development included vociferous discussions on the components of the prevention package, including whether to provide trial participants with access to VMMC (which was not widely available at the time) and STI treatment despite funding frameworks, for example:

"...in consultations during protocol development...the investigators felt very strongly that circumcision should be provided...and STI syndromic management...and, [the protocol chair] pushed very hard in that because the initial response was, 'We can't pay for this.' You know... we all agree that this is a fine idea but our funding is restricted to research. And, since ... circumcision and provision of STI syndromic

management, isn't part of our mandate. We can't fund that kind of thing. We'll have to figure out something else. But, you know, we can't really put it in the protocol because all of our funding comes from the [sponsor].' So, [the protocol chair] pushed very hard to have that added. And, pushed us very hard to find funding..." (Z9, network representative).

"...sites insisted on having a list of things available for their participants" (Z17, site staff, site 5).

Concerns raised by some respondents that being too demanding would serve to deter funders, did not appear to dissuade investigators from strongly advocating for the welfare of trial participants. Sponsors may be perceived to hold the upper hand in decision-making: they control the funding while investigators from resource-constrained contexts compete for that funding. This data indicates that investigators showed resolve in ensuring a state-of-the-art prevention package for trial participants. This advocacy from researchers to ensure a high standard of prevention further undermines concerns that researchers may provide substandard prevention interventions to ensure study endpoints (cf. McGrory et al., 2010).

2.1.4 The role of the network in standard of prevention decision-making

The network coordinated the protocol development process and was represented on the protocol writing committee. Respondents in this study sometimes conflated the funder/sponsor and the co-ordinating network. However, network representatives were careful to distinguish themselves from the sponsor:

"The way I understand it is that the X is in most cases the sponsor for our trials with some exceptions... Now in most cases the trial sponsor delegates to [the network] some of the authority, so some of the regulatory responsibilities and/or some of the operational responsibilities that a sponsor typically takes on.... and those responsibilities are delegated very clear in the arrangements between the [sponsor] and the [network]..." (Z9, network representative).

This distinction is ethically relevant because while the network must subscribe to and enforce the policies of the sponsor, they reportedly made great efforts to fulfil their moral responsibilities to participants. One possible reason for network representatives to highlight this distinction may have been to distinguish themselves from the practices of the sponsor some of which were criticised by respondents in this study.

In contrast to the somewhat negative portrayal of the sponsor in relation to funding policies, the coordinating network was reported to have made a significant contribution to ensuring

access to a high standard of prevention by securing alternate funding for a state-of-the-art prevention package, for example:

“...a lot of these trials are funded by federal government, and the US government has some quite strict rules about what they can and can’t fund, um, so, you know, where, aspects of the standard of prevention cannot be funded by the sponsor, other funds have to be found. Now, in the case of the [network], they might raise the money themselves. So, make the, you know, those funds available separately.” (Z18, site staff, site 5)

The network was perceived by some respondents as highly committed to ensuring a high standard of prevention both in terms of their role in decision-making and implementation:

“I can speak from personal experience with working with the [network]. They are extremely diligent in providing prevention services because they have made sure that we have implemented the male circumcision programme and then everything else... they are quite serious about it.” (Z7, site staff, site 1).

“Actually the [network protocol] is one of the best protocols I’ve ever worked on because you know they’ve actually paid for medical circumcision on the protocol and that’s quite expensive.” (C2, site staff, site 1).

Network representatives also reflected on the efforts initiated to satisfy standard of prevention requirements for the phase IIB study:

“So, I can tell you that at the time of protocol development we didn’t have any mechanisms in place to support the sort of two care elements there, the, the um STI treatment, and the circumcision....we had to negotiate. We had to find funding and negotiate for it because...it’s not part of the mandate from the [sponsor] and they can’t support it. So that required some hoop-jumping (laughs) but, um, not impossible...” (Z9, network representative).

“...I suspect what happens is it’s a discussion between very high levels of the [network] and very high levels of the vaccine manufacturer to say look this is something that the local investigators feel very strongly about. We’d like for you/ could you identify some money to basically /I cannot verify this in any way but my understanding is that our leadership goes knocking on doors to try and find the money.” (C10, network representative).

In this way, the network was able to navigate the complex terrain between satisfying investigators’ demands and meeting ethics guideline requirements while still honouring the sponsor’s mandate. It was anticipated by a network representative that these negotiations for alternative funding would become common practice for future trials, especially as new tools become available.

However, for the phase I trial, the network was not able to source alternate funding for VMMC or STI treatment and no reference to these prevention interventions was made in the ethical considerations section of the phase I trial protocol:

“Well, I can tell you that, for the largest trial that we’ve done so far in South Africa, we offered circumcision (R: Yep), um, er/ we’ve done a couple of low-risk trials since then, which, um::, we weren’t able to offer circumcision as part of this...” (Z9, network representative).

This suggests that standard of prevention determinations may depend on the phase of the trial. Distinctions in prevention options offered to participants in different trials are described in chapter 8 on the evolving standard of prevention in relation to relevant criteria for decision-making.

2.1.5 The role of CABs in standard of prevention decision-making

Community engagement has been defined as “a transparent and meaningful participatory process of stakeholder involvement in the trials process, from the design of protocols to the dissemination of results (UNAIDS/WHO, 2012, p. 17). Ethics guidelines also recommend the involvement of community representatives in designing risk-reduction interventions. Some respondents reported that CABs were represented on the protocol committee and on key network bodies, namely the ethics working group and the scientific steering committee of the network’s primary decision-making body:

“...in advance of protocol team meetings, someone from our office coordinates... discussions with the community members about what their concerns are, so that they are sort of collated, and coordinated in a way...” (Z9, network representative).

“...each site has its own community advisory board and they nominate one person from the community advisory board, from the local community advisory board to sit on a global community advisory board. So that G-CAB as we call it is made up of representatives from each site and then from the G-CAB we call upon a representative to sit on our sort of governing body. So that includes the protocol committee which is what reviews all concepts and all protocols; the scientific advisory group which reviews, it’s sort of a slightly different take on the protocol committee, they do slightly different reviews in terms of sort of scientific prioritisation so the protocol committee looks very closely at both.” (C10, network representative).

“I’m not sure how much the sponsors er, commit, but I know that our community representatives sit on those global boards, and they do, express the interests of their communities.” (Z11, site staff, site 2).

2.1.6 Complexities with stakeholder negotiation of the standard of prevention

2.1.6.1 Inherent power dynamics

One of the key challenges with authentically and meaningfully engaging communities in protocol development is the presence of an inherent power dynamic between scientists and the lay community (C10, network representative). In recognition of this potential imbalance of power, CAB representatives on the protocol committee were reported to have received network-provided support, including on the standard of prevention (see Chapter 11).

2.1.6.2 Perceptions of top-down decision-making

While some respondents in this study perceived protocol development to be a collaborative and inclusive process, other respondents expressed concern that decisions regarding the standard of prevention made during protocol development occur in a top-down fashion with minimal inputs from people on the ground such as site staff and CAB representatives. This criticism has previously been levelled against ethics deliberations, including on the standard of prevention (Heise et al., 2008).

For the phase IIB trial, it was reported that the protocol committee was not entirely representative of all implementing sites. By implication then, determinations on key standard of prevention decisions were not necessarily consultative and inclusive, for example:

“... what I’ve realised with [the phase IIB trial] was that basically you’d find that it will be the national PI who eventually would have done all that...when they come to other sites and then you find that basically the main negotiations have already been done” (C16, site staff, site 3).

“I have really no idea how we came up with that package. Uhm the [network] obviously came up with it. We didn’t really have an input in it.” (Z7, site staff, site 1).

“... how the whole um thing developed is that our site together with [site X] were the last ones to get on board and so, because I remember you know by the time our site was ready, the protocol was almost finalised” (Z22, site staff, site 1).

However, the involvement of selected sites/investigators was not deliberately exclusionary but reflected a practical challenge in that the participating sites may not all have been identified as early as the protocol development phase:

“...we have a face-to-face protocol team meeting although at that time, to be quite honest with you, some of the sites have not really been decided upon so it might be difficult to, at that point in time, get input from the local investigators because they’re

not, they haven't actually generally been picked for the trial..." (C13, network representative).

Most CAB respondents perceived a more limited role for the CAB in making substantive inputs into standard of prevention determinations generally, and particularly regarding decisions taken during protocol development. This may relate to the way in which community representatives were selected to be on the protocol committee:

"...typically we start with that chairperson's site, identifying the community member and staff member and CAB representative. But, if no one from that site is available, then we branch out." (Z9, network representative).

Rather than a sense of inclusivity, selecting a CAB representative from one or two sites to be on the protocol committee, fostered a sense of marginalisation amongst some CAB respondents. It highlighted that these particular CAB members did not enjoy the same levels of engagement and involvement in HVT decision-making as CAB members at other sites, for example:

"....it [the protocol] came as final deal, as a done deal to them." (Z2, site staff, site 1).

"The CAB has complained they were not involved in the protocol. [The PI] explained that we were the last site to be involved in [the phase IIB trial] and not even the researchers had input....But other sites seem to involve their CAB more...one member is in the scientific protocol development team, another on ethics team" (C1, site staff, site 1).

"You know, we've got the theory part and the practical part, huh? The theory part is that you develop the protocol with them [the community], but practically, as you may be aware that, these protocols are developed at a very high level" (Z11, site staff, site 2).

"As you say, at the moment our PI's are having to consult communities. I guess, you know, the criticism is it's after the fact. You know, you're presenting them with a protocol. You know, you're not going in and saying let's develop a protocol, which I think does have very practical problems." (C6, REC).

Some CAB respondents expressed a strong desire to be involved in decision-making and at one site, a request was made of a fellow researcher to facilitate the involvement of the CAB on the local REC.

2.2 Defining the standard of prevention in protocols (the what)

Ethics guidelines make specific recommendations for the protocol regarding the standard of prevention. Both MRC (2003) and UNAIDS/WHO (2012) guidelines require that risk-minimisation measures should be outlined in the study protocol.

In line with ethics guideline recommendations, the standard of prevention was defined in the ethical considerations section prefacing both study protocols. The phase I protocol specified that risk-reduction counselling would be provided to participants. No other prevention interventions were specified. The phase IIB protocol stated that the research network *is committed to ensuring that all trial participants receive access to the highest standard of prevention which may include, but is not limited to, access to risk reduction counselling, provision of male and female condoms, access to syndromic management of STDs, information regarding male circumcision and referral to services that can provide male circumcision and post-exposure prophylaxis when indicated*.

Neither protocol however, delineated mechanisms for stakeholder negotiation regarding standards for enhancement of the risk-reduction package as per UNAIDS/WHO (2012) specifications.

Apart from the statement in the ethical considerations section, there was little other detail in protocols regarding the standard of prevention, including regarding the implementation of the prevention package, except that VMMC should be provided via referral. This silence was initially flagged as problematic during the document review process. However, it became increasingly clear during interviews that the statements on the standard of prevention were appropriate and well considered, including the lack of detail regarding how best to implement prevention services at sites. Such detail was argued to necessitate additional levels of oversight and monitoring as well as a consistent approach to implementation across sites, despite different socio-cultural and economic contexts *“if you prescribe it in the protocol, any deviation from that is an actual deviation from the protocol”* (C14, network representative). Rather than in protocols, such details were reportedly captured in documents such as the manual of operations.

Given the changing HIV prevention landscape, the sponsor/network did not have an established policy on the standard of prevention. Instead, the standard of prevention was

determined on a *protocol by protocol* basis. Defining the standard of prevention in the ethical considerations section of the protocol was reported to ensure that it was debated and discussed during the protocol development process. Respondents *au fait* with the protocol development process highlighted that the standard of prevention, and other ethical issues, were considered as important as the science, and that the ethical considerations section was interrogated to the same extent and with the same rigour as the rest of the protocol.

“The ethical considerations...that section will be evaluated just as carefully as the statistical section, as the procedures section...that one line that you were reading from the ethical considerations section [referring to the standard of prevention]...that is where we put it to ensure that that discussion comes up in the protocol...in other words, we didn’t put it in an SOP at the sites, we didn’t put it in a policy statement that isn’t reviewed by every protocol, we put it right in the protocol so that it is reviewed by everybody... (Z9, network representative).

2.3 Defining the standard of prevention in informed consent forms

With regard to informed consent, MRC (2003) and UNAIDS/WHO (2012) both require that risk-minimisation measures should be detailed in the ICF. Further, participants should be counselled that they will receive access to risk-reduction counselling and proven prevention interventions (MRC, 2003; UNAIDS/WHO, 2012).

ICFs for both studies specified that prevention counselling would be provided to participants to help them avoid getting infected with HIV. However, ICFs provided no information about access to other prevention interventions. It was reported that this may either be an oversight or deliberate to allow for flexibility in REC review, for example: *“the other thing we don’t want to do is be too specific so, every time there’s a change to the consent form, obviously it has to go back to the ethics committee for review”* (Z9, network representative).

While ICFs do not meet guideline requirements in terms of defining the standard of prevention, interviewees reported that the prevention package was described to participants in the informed consent process.

This data indicated that with regard to the content of ICFs, practices deviated from guideline recommendations. Sites provided substantially more to participants (see Chapter 9 on implementation practices) than was specified in ICFs. Concerns that providing detail on standards of prevention in these documents would curb flexibility in REC review is not

predicted by ethics guidelines, which instead underscore the importance of full disclosure to RECs.

2.4 Comparison of protocol development practices with ethics recommendations

The standard of prevention for both trials was largely determined by the protocol writing committee, which included representatives from the sponsor, the coordinating network, and selected trial sites and host community representatives. This resonates with requirements in ethics guidelines that HIV prevention packages be negotiated by the research team and relevant stakeholders during the protocol development phase (cf. UNAIDS/AVAC, 2011) and that the community participates in protocol development (cf. MRC, 2003; UNAIDS/WHO, 2012). While ethics guideline requirements were generally satisfied, several challenges were reported regarding standard of prevention determinations during protocol development, particularly pertaining to funding and community involvement.

The potential for sponsor policies to impact on standards of prevention have been reported in other empirical studies. Philpott et al. (2010) found that donor policies that restricted how research funds may be used, limited the level of care provided to trial participants. Ethics guidelines too (UNAIDS/AVAC, 2011) acknowledge that potential funding restrictions may influence the provision of a comprehensive standard of prevention. To this end it is recommended that when funding-body restrictions limit which prevention methods can be paid for by trial funds, research teams have the responsibility to find other ways to provide these methods, such as through alternative funding streams or linkages with non-governmental organisations or community-based organisations (UNAIDS/AVAC, 2011, p. 49).

Consulting the community on protocol development and informed consent has been argued to have protective benefit for communities (Weijer & Emanuel, 2000) and is entrenched in ethics guidelines. The most common mechanisms for achieving community inputs in HIV vaccine research is through CABs (Boulanger et al., 2013; Marsh, Kamuya, Rowa, Gikonyo & Molyneux, 2008; Morin et al., 2008). While it could be argued that ethics guideline requirements were satisfied by the involvement of selected CAB representatives on the protocol writing committee, some respondents did not equate this representation with meaningful community participation. While ethics guidelines require community inputs on the standard of prevention, they do not delineate the process for such engagement so it was

perceived by some respondents that the engagement mechanism of involving selected CAB representatives was inadequate.

Perceptions of inadequate community engagement in this study are consistent with previous findings. An exploration of the role of CABs in health research in South Africa (Reddy et al., 2010, p. 6), found that "CABs had limited influence on the substantive decisions of the research project." The standard of care mapping study at microbicide trial sites, including South Africa, also found that at all sites, except one, community members and advisory groups were not consulted about the prevention package before protocols were approved. Their input was occasionally sought when the protocol had already gone through the approval process (Heise et al., 2008). Findings from the present study are also consistent with research that identified stakeholder input in trial protocols as a gap between GPP guidelines and site practices (Hannah et al., 2012) and which found a perceived low relevance of GPP guidelines regarding stakeholder engagement in both protocol development and the standard of prevention (Ngongo, Priddy, et al., 2012b).

The lack of community engagement on standards of prevention during protocol development found consistently across studies, begs the question of why this ethics requirement is not realised in practice. While the reasons for this discrepancy between guidelines and practices have not been elaborated upon in previous empirical studies, this study found that there were practical challenges with meaningfully engaging all communities on the standard of prevention in trials. The thorough engagement of all affected CABs was constrained by the fact that not all sites were selected as implementing sites prior to the protocol development stage. This challenge is anticipated in guidelines (UNAIDS/AVAC, 2011) which state that in some instances opportunities for community input during protocol development might be limited.

3. Protocol review practices and perspectives

While decisions about which prevention interventions to include in the standard of prevention predominantly occurred at the protocol development phase, protocol review presented an opportunity for the HIV prevention package to be "vetted" by other research stakeholders (Z18, site staff, site 5).

Once the protocols were developed, they underwent sequential scientific and regulatory review by the sponsor. The sponsor provided comments on the protocols and the research network coordinated responses from the protocol team, including “*community representatives and site level representatives*” (C10, network respondent).

The master protocol and supporting documents, including template ICFs, were then sent to sites. Before implementation at sites, protocols were submitted to several bodies for review, namely CABs, RECs and the regulatory authority (the MCC).

The document review process found no substantive differences between master protocols and site-specific protocols for the two trials, suggesting that few amendments were made to these protocols before being distributed CABs and RECs for review.

The prevention package offered in the two trials (see Chapter 9) indicates a discrepancy between what was provided to participants in trials and what was spelled out in both ICFs and protocols. Essentially this implies a disjuncture between what CABs and RECs approved as the standard of prevention and what was actually provided in trials. This may not be ethically concerning since the standard provided to trial participants exceeded what was committed to paper. Protocol and ICF drafting practices reported in this study do not align with the perspectives of REC stakeholders at the Ugandan consultation (McGrory et al., 2010) which argue that researchers must be explicit about how often the risk-reduction intervention will be provided to participants, the study staff responsible for delivering the service, and the required infrastructure. However, given ethics guideline recommendations that RECs should approve the risk-reduction package, it is especially pertinent that all the available information is provided to RECs, in a way that still permits flexibility for researchers. Failing this, RECs would have to approve amendments to the protocols.

CAB and REC members were interviewed on their practices and perspectives pertaining to the review of HVT protocols, particularly concerning standard of prevention considerations.

3.1 CAB review of protocols

Ethics guidelines recommend that community representatives participate in the review of the trial protocol (UNAIDS/WHO, 2012) and make inputs into the informed consent process (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) to ensure that the research is

informed by the concerns and priorities of the community in which the study is to take place (UNAIDS/WHO, 2012, p. 23). Protocol review presents another opportunity for community representatives to make inputs into the design of the standard of prevention as required by guidelines (cf. MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

In efforts to involve the community in all phases of the research process, CABs were involved in the review of study protocols/protocol summaries and informed consent materials. Two primary purposes of CAB review of protocols were identified in interviews. Firstly, review allowed for CAB oversight of research, ensured that the protocol represented the community's interests, and was ethical:

"...before we even go out to a community, we actually get them [the CAB] to go through the protocol. Together with them, we do a community diagnosis or community mapping to say what are the feelings, what is the feel, what is the attitude out there, you know for the community" (Z8, site staff, site 4).

"Particularly with the history of research, we all know how people were, were used and hurt, in the name of getting successful researches... hence the involvement of the community in research and the informed consent to say everybody must be aware of what is being researched and how it is going to be done so that at the end of it all, things are done ethical, that is to say things are done in a way that nobody gets hurt in the name of research." (Z3, CAB, site 2).

It was argued that community oversight of research was critical in helping researchers maintain ethical standards, especially with regard to ensuring that researchers "don't over-research" (Z3, CAB site 2).

Secondly, protocol review developed CAB competency on the protocol which facilitated their community education and outreach activities. In addition, the review of protocols and/or ICFs also enabled CAB oversight on ethical issues related to protecting the interests of the participants (Reddy et al., 2010, p. 3) and ensured community representativity on issues pertaining to the standard of prevention.

While many of the CAB respondents could detail their concerns regarding issues of HIV care and treatment, the standard of prevention was not consistently noted as a concern by CAB respondents nor was it described as a critical element of the review process. The complexities with review, particularly regarding the standard of prevention, are described below.

3.1.1 Complexities with CAB review

3.1.1.1 CABs' perception of review process as tokenistic

Perceptions about the CABs' ability to impact on and meaningfully contribute to decision-making during protocol review were mixed. CAB representatives at most sites felt that the protocol review process provided an opportunity for them to interrogate the protocol and accompanying documents and that their recommendations were seriously considered. Rather than aspects relating to the standard of prevention, most CAB interviewees described that they scrutinised the eligibility criteria, risks and benefits, and the language and wording of ICFs. The focus on the latter issues was in line with the specific roles and responsibilities identified for CABs (NIAID, 2009).

A CAB representative at one site reported that despite the imperative to involve the CAB in the review of all study protocols, there was an uneven approach to engaging CABs in protocol review, with the CAB only reviewing selected protocols. Opportunities for review may vary by trial, especially in multisite trials (UNAIDS/AVAC, 2011) like the phase IIB trial where protocol development was a largely centralised exercise. It has also been acknowledged that "extensive grassroots consultations prior to conclusion about the content of the standard of prevention packages for research may not, and indeed cannot, always occur" (Haire et al., 2013, p. 6).

At another site, the review of protocols was perceived by some as tokenistic "undertaken merely to tick the relevant boxes of community engagement. It was reported that the CAB felt that they had little power to demand changes to the protocol because CAB and REC reviews occurred concurrently:

"The CAB is not involved in developing the protocol, and the CAB has no power to change things – the protocol has already been sent to ethics" (C1, site staff, site 1).

"...it's already in the protocol by the time you send it out to the community to review what you've already written." (Z5, site staff, site 2).

The review of ICFs accords with CAB insider-knowledge of the community and their understanding of the dynamics and nuances of the community. Such review contributes to culturally astute informed consent processes and effective health research. Despite community representativity on RECs, there were reports that CABs identified issues with

ICFs that were not always recognised by RECs, indicating their critical role in the review process.

Despite concerns that concurrent review by CABs and RECs may result in the contributions of the CAB being overlooked, it was reported that relevant CAB concerns have resulted in amendments to the protocol, even post REC approval:

“...half the time this [CAB review of protocols] happens at the same time that your research ethics is reviewing the protocol. But what has struck me, in fact what I like, is that we have these multi-site, you know, trials. And, the protocol goes to your [X REC], it goes to your [Y REC], and goes to your [Z REC]. We’ve had the community’s inputting onto the protocol, such that we had to change. It didn’t matter which site you were at, that they look at this and say, ‘This cannot happen this way.’ And it’s impacted on all. Some of the protocols had already been approved by the research ethics, but once the communities read this, the various sites had to put their heads together to say, ‘This has come up, and they think we need to look at this and we need to change’. So, ja, as much as the theory says, at the development, they come in very late, after the protocol has been developed, but I’ve observed that they still have an impact on/ ja.” (Z11, site staff, site 2).

Some CAB representatives have problematised their role as the link between researchers and communities by arguing that certain site-level decisions, including the name of the CAB, negatively impacts on the ability of the CAB to protect the interests of the participating community:

“There is a big tension here about the brand-name – it is called a CRSG – a Community Research Support Group. There have been questions about this – why this name? The answer was “advisory” and “board” means that they can say no and nothing will happen! CRSG implies support for the researchers. I was trying to probe this issue. To me, they are the advisory board. They advise on community values etc. The power of advising has been taken away.” (C1, site staff, site 1).

At another site, the term advisory was perceived as not all-encompassing but limited to their expertise on the community: *“...the advisory don’t advise the researchers on what research to do, but we tell them about the nature of the community.” (Z3, CAB, site 2).*

The quality of the relationship between sites and CABs differed across sites. At sites where CAB members enjoyed a close working relationship with site staff, including the PI, their perceptions of their engagement was more positive. Good relationships between PIs and CAB members have been reported as a critical element of effective CAB functioning (Strauss et al., 2001).

Another key concern expressed by most CAB respondents related to their ability to serve as a “watchdog for the participant so that participants are not abused or taken for a ride” (C21, REC). At most sites, CABs were denied access to trial participants by sites with the view to protecting participants’ confidentiality. Again, this was perceived as limiting the role of the CAB in terms of advocating for trial participants:

“...the CABs are there to ensure that the trial participants are not abused or exploited ... But on the other side, there is this big word confidentiality which blocks the whole relationship now. It says black and white that you there as an advocate, but then again in practice, the trial participant is not given a chance due to the confidentiality issues that they talk about, that they cannot discuss these matters with the CABs, they cannot meet with the CABs in person. So we don’t know when really in practice you become an advocate.” (Z1, CAB, site 1).

The fact that the CAB was often called upon when the site experienced major challenges and “something that has exploded” (Z1, CAB, site 1) may have surreptitiously conveyed to CABs that sites determine the CABs’ oversight role and that mostly, it was their role in support of research that took precedence. At the one site where CAB access to participants was permitted (after signing confidentiality agreements) and highly regarded, the CAB respondent reported a positive relationship with the site: *“What works well is that you know as CAB members we do follow up to participants.” (Z3, CAB, site 2).*

3.1.1.2 Disengagement of CABs

Still for other CAB respondents, review of protocols did not appear to be a priority. These respondents found it difficult to describe whether they have reviewed protocols and ICFs, and what they looked for during the review. These ambivalent perspectives suggest that individual CAB representatives may have different conceptions of their roles. For some CAB representatives, their role in supporting research took precedence over their role in advocating for trial participants. This disengagement by some CAB members was also articulated by a site staff member at one site:

“I think the community advisory boards play a really important role within the function of the site. We certainly you know uh hold them in high regard...they have a real status and um we provide them with whatever support they need to function. However uh under the life span of a site, CABs go through good times and bad times and uh you know we have our fair share of those. Um so it’s great when the CABs are committed, energetic, enthusiastic, supportive, engaged it’s wonderful uh but when they are disengaged, uninterested, uh don’t care um and I’ve got into big trouble from when I dared suggest that CAB members just come to eat the food/[for] a pair at our site we thought that was certainly true and they’d arrive just at the end of the meeting

so that they could be counted and get access to the food provided just afterwards um so but that's the life of a CAB uh and that's not unexpected" (C18, site staff, site 4).

At another site a CAB respondent noted that the negative results from the phase IIB trial and the consequent reduction in the frequency of CAB meetings, were discouraging for the CAB and *"the morale of the CAB took a dip"* (C12, CAB, site 3). Given that the medical and scientific experience of individual CAB members differed widely, infrequent meetings may reverse any gains in research literacy.

Some CAB members also expressed some dissatisfaction with static reimbursement allowances not on par with inflation, as well as with the lack of a budget for CAB activities including community education workshops.

3.1.1.3 CAB understanding of scientific concepts

To meaningfully contribute during the review process, CAB members were trained to review protocols and received support for this task from sites. This resonates with ethics guideline requirements (MRC, 2003) to build the capacity of community representatives to contribute to the development and review of HVT protocols. However, such site-provided support is criticised as potentially tainting CAB independence (Koen et al., 2013). Given that CAB involvement in research, albeit voluntary, provides them with otherwise scarce opportunities for capacity building and travel, CABs may be unlikely to criticise a study, even when such criticism is warranted (Koen, 2010). By virtue of being supported and educated by sites, there was also some concern that CABs could be perceived as potentially biased towards the research organisation (Koen et al., 2013). Nevertheless, the present study found that CABs were free to, and often did, consult external experts on aspects of the protocol at their prerogative.

It was reported that CABs may experience challenges in understanding some of the scientific concepts described in protocols, which may impede their review of standards of prevention. The standard of prevention is intimately related to the science of the trial and the background prevention package impacts on the statistical power of the trial and efficacy determinations. Such statistical concepts are complex to understand:

"You're having to work with probabilities... people aren't understanding what actual implications...unless you have got a fairly good sophisticated understanding." (C6, REC).

CAB respondents concurred that some scientific concepts were difficult to comprehend. Even during interviews, CAB representatives demonstrated some confusion regarding these issues. Most were unclear about the standard of prevention implemented at their respective sites despite having reviewed the protocol and consent material.

3.1.1.4 Cultural taboos

CAB discussions regarding components of the standard of prevention were sometimes hindered by cultural norms and practices. Discussing sexual activity and related issues among CAB members of different genders was argued to be inappropriate, for example:

“...in our culture we can’t talk something like that too much because if we are around the men they can’t talk with those things” (Z19, CAB, site 4).

“...it’s difficult [to discuss male circumcision]. The other person doesn’t want to speak in front of a peer that’s a girl.” (Z21, CAB, site 5).

“Uhm it’s not a usual thing in our community... it’s also the norm that women don’t talk to men about it [circumcision]” (Z17, site staff, site 5).

The need to challenge some cultural prescriptions was noted and it was argued that communities need to be empowered *to openly talk about these things...So unless we make these talks open in all our institutions, we really gonna take a while before we are there”* (Z5, site staff, site 2).

3.2 REC review of protocols

All ethics guidelines mandate the ethical review of research protocols (cf. MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). RECs review protocols to determine whether they meet ethical and scientific standards for conducting research with human participants. The REC has the power to approve, request modification, or disapprove a research protocol. Independent review is one of eight principles identified for conducting ethical research in developing country contexts (Emanuel et al., 2004). This entails mandatory review by bodies without stake in the research, such as RECs and regulatory authorities. RECs were perceived by site staff and network representatives as critical stakeholders in the oversight of study protocols, including regarding the standard of prevention.

Ethics review of HVT protocols typically considers the prevention package that will be promoted in trials in order to comply with ethics recommendations as well as with the scientific imperative to determine the safety and efficacy of the experimental vaccine against the background of established, ongoing or planned prevention modalities (Tarantola et al., 2007, p. 4865). Ethics guidelines require that RECs approve the standard of prevention (MRC, 2003) as well as plans for monitoring risk-reduction interventions (MRC, 2003; UNAIDS/WHO, 2012).

REC respondents described that when reviewing protocols they generally considered the *“presence or absence of risk-reduction”* (Z16, REC). In addition, some REC respondents reported that there was a minimum standard of prevention that must be provided to participants in HVTs, namely condoms, STI treatment and risk-reduction counselling. This is on par with the minimum standard of prevention offered in most HIV prevention trials (cf. McGrory et al., 2010). REC respondents reported to rarely weigh in on the intricacies of the standard of prevention but reported occasionally influencing standard of prevention implementation practices: *“...we were one of those who actually pushed for the syndromic approach”* (C21, REC). The two protocols reviewed in this study did not specify plans for monitoring risk-reduction interventions and REC interviewees confirmed that they did not review plans for monitoring risk-reduction interventions. More often, RECs required assurance that researchers would take steps to help keep participants HIV-uninfected and paid less attention to the actual components of the package or related implementation practices. These findings conflicted with assertions that RECs expect researchers to specify *“the frequency, mode, and personnel responsible for delivering the service and the infrastructure used”* (McGrory et al., 2010, p. 17).

REC respondents generally reported having an excellent working relationship with South African HVT investigators developed on a foundation of trust that investigators *“completely want to do the right thing in terms of standards of prevention”* with the affirmation that *“... I haven’t had in...my years of being the chair of the committee any acrimonious arguments around standards of prevention issues”* (C19, REC). Investigators too, described the relationship with RECs as good and founded on *“good communication and mutual respect”* (C11, site staff, site 5). It was described that in some circumstances investigators have approached RECs prior to protocol development regarding challenges with sponsor policy in order to *“flag what they think we...would have a look at”* (C17, REC). In cases where

sponsors and other stakeholders are unwilling to commit to providing a high standard of prevention, such prior discussions may prompt RECs to probe this reluctance.

3.2.1 Complexities with REC review

3.2.1.1 Applying variable standards in reviewing protocols

One challenge in meeting ethics guideline requirements of approving the standard of prevention package was that REC respondents reported applying variable standards in the review of protocols. Essentially the level of review was reported to be dependent on the quality of the members present at the particular meeting, for example:

“I wonder if we don’t tend to apply relatively uneven lenses or uneven standards in critiquing protocols and what we expect out of protocols... I think the REC standards are themselves quite variable, and that’s not malice or to slight the REC it’s just, it depends on who reviews it and who’s at the committee meeting on that day and how interested they are.” (Z16, REC).

“Uh to be quite frank we’ve got nothing laid down. I think it’s really an ad hoc response of the people at the meeting at the time” (C17, REC).

“...there isn’t a specific thing that a committee would look for...” (C19, REC).

3.2.1.2 Lack of ethics capacity on RECs

Other reasons purported for this variability included a lack of capacity as well as resource and time constraints, which inhibit the ability of RECs to interrogate major substantive issues as rigorously as they should:

“...we are not educating...our committee members, you know we’re falling very short there. You know, we’re busy educating everybody else, (laughs) but not locally... unless you’re familiar with the UNAIDS guidelines, you don’t know what is expected really and we are back to this issue of nit-picking informed consent forms. You know, too much time is spent on that sort of thing as opposed to the really substantive ethical issues” (C6, REC).

“...usually you find many of the people who serve on the ethics committee don’t have ethics training... whatever they’ve learnt about ethics is what they’ve just read about or come across by chance or by doing their own literature review search. But you know if you are doing your own literature review search... if you don’t know what ancillary care is you’re not going to go and look for ancillary care, and find out what it means. So, I think that, in the context of RECs in South Africa and elsewhere, it depends on who the member is, and what their training is, and so you’ll find that, in my opinion, it widely differs...” (Z12, REC).

“...it depends on the skill of the reviewer as to how much of that is picked up...we would send to expert reviewers in the field, who mightn’t pick up or make issues out

of the ethical issues of referral. That would have to be picked up by the committee, which has only read often the synopsis, at a full committee meeting. So unless I have made an effort to look, or somebody picks it up, it might fall between the cracks.”
(C6, REC)

3.3 Comparison of protocol review practices with ethics recommendations

Community representatives and local RECs are required to review HVT protocols and informed consent materials regarding the standard of prevention and the monitoring thereof (cf. MRC, 2003; UNAIDS/WHO, 2012). In congruence with ethics guideline recommendations, it was reported that for both trials, community representatives (in the form of CABs) and RECs reviewed the protocols and related consent materials. However, practices deviated from guidelines in terms of REC review of risk-reduction monitoring plans ó such plans were not included in protocols or ethics applications.

In terms of protocol review, several complexities with CAB review were noted including the perception of the review process as tokenistic, the disengagement of some CAB members, a lack of research literacy and understanding of science as well as cultural taboos (see Chapter 11). Ethics guidelines address some of these identified concerns. The need to build research literacy as an essential component of stakeholder engagement is recommended by guidelines (UNAIDS/AVAC, 2011). While engaging community stakeholders is argued to increase the socio-cultural relevance of the research (Boulanger et al., 2013; Marsh, Kamuya, Parker & Molyneux, 2011; Tindana et al., 2007), guidelines do not anticipate that cultural taboos may deter key standard of prevention considerations. These socio-cultural norms and practices create tension in terms of the CABs' role in making inputs into the design of the standard of prevention and deserve further detailed exploration.

REC review of standards of prevention in protocols and ICFs was limited to ascertaining the presence of such a package (see Chapter 11 for detailed discussion).

4. Protocol implementation practices and perspectives

The standard of prevention was determined during protocol development and approved during protocol review. However, for the phase I trial conducted at two sites, the actual standard of prevention provided to participants in the trial exceeded the determined and approved standard of prevention (see the Chapter 9). Furthermore, for both trials, several factors during implementation impacted on the actual standard of prevention provided to

individual participants. These factors included site-level decisions, provider decisions to promote services and participant decisions to take up services. These are briefly described below.

4.1 Site-level decision-making

To some extent, decisions on the standard of prevention were made on a site-by-site basis. More experienced sites, with better finances and/or well-developed referral networks, reported having an established standard of prevention which they were able to offer all participants regardless of what was outlined in the protocol and/or funded by sponsors:

“...are we going to make the standard of prevention, countrywide? And, what is going to be the standard of prevention for our research protocols? Um, and is that going to be community-specific? Or is that going to be country-specific? Or is that going to be protocol-specific? And so I think, you know, um, I’m not sure that I have all those answers at the moment. I mean, currently, there has been a level of site-specificity to this... to illustrate this I will put as an example iPREX. So, the iPREX MSM study that we’ve just participated in, the standard of prevention that was offered in the protocol was, condom, you know, male condoms, lubrication, regular testing with risk-reduction counselling... We then mentioned that we have in our standard of prevention, post-exposure prophylaxis. And it was agreed that we could offer post-exposure prophylaxis, even though that was not across all sites...So, I thought it was a nice example of how a protocol, um, modified itself, if you like, to take into account a site’s own standard of prevention.” (Z18, site staff, site 5).

The network also acknowledged permitting some site flexibility with regard to standard of prevention implementation.

“...because we don’t know the capacity of each site...our template consent is phrased in a way that is um you know is basically for the site that cannot provide that but rather will refer for that um and sites are always free to change that consent and make it site specific and if they’re able to do that that’s more power to them” (C13, network).

While for some respondents, site-level decision-making enabled the individual nuances of each trial context to be accommodated, others contended that it created unwelcomed differences between participants enrolled in the same trial at different sites (see Chapter 11). Recommendations in UNAIDS/WHO (2012) ethics guidelines were intended to minimise double standards between developed and developing countries (Macklin, 2009; Haire et al., 2013) and indeed some respondents have argued that this was achieved for the phase IIB trial: *“They are providing first world care in a developing country...”* (Z7, site staff, site 1). However, actual practices at sites may inadvertently perpetuate double standards between better-resourced and less-resourced sites within the same country.

In contrast, some respondents perceived that there was an existing established standard package of prevention which was a routine part of the protocol (Z5, site staff, site 2):

“... there’s now kind of a standard that everybody has to comply to...It’s kind of we do standard things that people know, it doesn’t even get discussed, it must be in, in the protocol.” (Z17, site staff, site 5).

“...there’s all of these things that are part of the package and that’s how it will stay. I suppose the way to address your question is to say what’s next, ‘cause we aren’t going to peel things off” (Z6, site staff, site 2).

Despite the perception by some that protocols complied with an established standard of prevention, the standards of prevention outlined in the phase I and phase IIB protocols were distinctly different. It was suggested by a network representative that in future, the implementation of standards of prevention may be systematised and formalised to ensure uniformity as the number of South African sites expand for a large-scale efficacy trial of the Thai RV144 vaccine (cf. Esparza, 2013).

4.2 Provider decision-making

Providers have a central role in determining which prevention interventions were actually offered to participants. Provider-promotion of components of the standard of prevention is a focus of Chapter 9 on standard of prevention implementation practices. It was highlighted that some providers may suffer a general apathy towards ensuring the well-being of participants, may exercise their own preferences in counselling participants on certain prevention modalities, or may be inadequately trained:

“...if the very people that are supposed to give it don’t know much about it, it’s pointless. We give information to the communities, and the communities are so bright and they know about these and they get there, and people are looking at them like, huh? The same thing happened with female condoms. The female condoms expired in storerooms (laughs).” (Z11, site staff, site 2).

“... at whatever site you are at there are healthcare nurses, they can’t make a diagnosis. I think it’s got to do with maybe laziness or lack of insight, or no innovation happening at a site level.” (C4, site staff, site 2).

“Another thing which perhaps I think is important is the person who gives these people the preventative measures, whether the person is properly or was properly trained...Now to some extent measures might fail not because of the participant but because of the people who deal with the participant. So you have to question yourself time and again. You just say they are wrong, you don’t know, you were not there when you know they trained, you were not there when they offered these condoms to

the person but you don't know what really went on. There's no way, there's no criteria, there's no way you can check ...” (C12, CAB, site 3).

As the available prevention arsenal expands, it was described that there may be increased opportunities for providers to play a more active role in standard of prevention decision-making at an implementation level 6 by tailoring prevention packages to suit individual participant's needs. This would involve customising the standard of prevention to carefully developed risk-profiles of participants 6 in a manner analogous with women choosing the best contraceptive method from a basket of options.

“Then of course, um, there's the whole piece of deciding well, what would be a good, prevention package for this individual. And, so how do I tailor my risk-reduction counselling, or my prevention package for this individual, is the next step. And I think, this is probably because we have only recently moved in the paradigm, of understanding that, you know, it's not just A, B, C for everyone...So, I think as we move more strongly into a paradigm of prevention packages, um, healthcare workers are going to have to become, um skilled at deciding which package is best for an individual, and an individual is going to have to be skilled up, to be able to, you know, help make those choices, or decide what's best for them. ...you can either present a set menu, or you can present an à la carte menu, and so the individual may pick and choose what they think is going to work for them, with your guidance. Or else you'll say, you are a young adolescent with the following risk profile, I suggest you use the following, you know...” (Z18, site staff, site 5).

4.3 Participant decision-making

Ultimately, the individual trial participant decides which prevention services to take up. Issues pertaining to participant uptake of specific prevention services are described in Chapter 9. Of critical importance to participants' overall decision-making ability, respondents across stakeholder groups emphasised participants' autonomy in making decisions in line with their personal values and preferences, for example:

“...it can't be forced on anyone anyway... you can provide it, but...there's no guarantee anybody's going to definitely use it, or want to take it up” (Z12, REC).

“...you still have the people that are not going to be using, even if it's available and accessible...” (Z11, site staff, site 2).

“...you offer it, you offer the best, and if, um, it is up to them to either refuse or accept it” (Z10, site staff, site 5).

“...on the other hand it's important that you know not everybody's the same, you know so people have different beliefs and different preferences. So it is important to have different things available for people to access.” (Z17, site staff, site 5).

Enabling participant preferences in terms of which prevention options to take up is in line

with the ethical principle of respect for autonomy (see Chapter 11).

5. Summary

This chapter addressed the research question of the extent to which actual standard of prevention decision-making practices correspond with related recommendations in ethics guidelines. In resonance with the literature, none of the respondents in this study argued against the provision of a standard of prevention package. Rather, respondent perspectives on the rationale for providing risk-reduction interventions to participants were diverse and many individual respondents articulated multiple rationales.

Data from this study indicated that the primary standard of prevention deliberations occurred during the protocol development process. The protocol committee was positioned as the leading decision-making body with regard to establishing the standard of prevention package for every trial. The standard of prevention was also approved during protocol review. At these phases, sponsors, investigators, communities and RECs had the opportunity to make inputs into the design of the standard of prevention. Given that these different stakeholders represent different interest groups, the determination of the standard of prevention during protocol development was fraught.

Some respondents across stakeholder groups perceived the sponsor as dominating decision-making, particularly in relation to intractable sponsor policies on funding for research. Investigators on the other hand were perceived as strong activists protecting the welfare of participants in stark contrast to the perception by a few that they need independent monitoring to ensure their compliance with ethical norms. The network was viewed as committed to ensuring a high standard of prevention in trials by securing alternate funding for the standard of prevention.

There was a disjuncture between community representatives' perceptions of their impact on the standard of prevention during protocol development and review versus perceptions of their involvement by sponsors and researchers. The lack of inclusivity of all sites in decision-making processes has had the unfortunate yet predictable result of some CAB representatives feeling alienated and disengaged from the decision-making process. While CABs sought more decision-making authority, RECs possessed such power but did not necessarily appear to maximise it for the standard of prevention.

REC review practices did not wholly satisfy ethics guideline requirements in terms of approving the standard of prevention and plans for monitoring prevention interventions. Several complexities were described in meeting these recommendations including a lack of set standards for critiquing protocols and a lack of ethics capacity on RECs which favours the discussion of procedural rather than substantive issues.

Major thematic complexities of power, partnerships/funding and culture will be examined in the discussion (Chapter 11). The following chapter will focus on the critical and relevant factors that were considered when making decisions on the evolving standard of prevention.

CHAPTER 8

THE EVOLVING STANDARD OF PREVENTION: DECISION- MAKING PRACTICES AND PERSPECTIVES

The preceding chapter detailed respondents' standard of prevention decision-making practices and perspectives. This chapter presents respondents' practices and perspectives regarding the evolving standard of prevention, and focuses on the criteria respondents considered relevant when making decisions on adding new tools to the prevention package. Data in this chapter were analysed using critical thematic analysis (Braun & Clarke, 2006) which, where relevant, involved consideration of discursive undertones. Decision-making practices and perspectives were compared with relevant HIV prevention recommendations in ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), and decision-making frameworks (Jay et al., n.d.; Philpott et al., 2011; Tarantola et al., 2007), where relevant.

1. Criteria for the enhancement of the standard of prevention

With every positive HIV prevention trial outcome, there is increasing concern about standards of prevention, particularly regarding how and when to add new tools to the prevention package (Essack, Slack, et al., 2010; Haire, 2014; Macklin, 2009; McGrory et al., 2010; Philpott et al., 2011). During data collection, positive results for topical and oral PrEP trials became available. In addition, the treatment as prevention trial (HPTN 052) demonstrated the success of early ART initiation among serodiscordant couples. Amidst these positive results, the FEM-PrEP trial designed to assess the efficacy of daily oral Truvada among women was closed for reasons of futility, as were the oral Truvada and the Tenofovir gel arms of the VOICE trial (Hankins & Dybul, 2013). In July 2012, just prior to the conclusion of data collection, the FDA approved Truvada for use as an HIV prevention drug for those at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners (FDA, 2012). At the time, the South African regulator (the MCC), had not reviewed the data nor approved Truvada for use as an HIV prevention intervention.

As the available prevention arsenal increases, some commentators have recommended that efforts be made to understand how decisions are made on the enhancement of the prevention

package (Essack, Slack, et al., 2010). To this end, respondents were asked their perspectives on the criteria that should be considered when adding new tools to the standard of prevention. While positive HIV prevention trial results were largely welcomed by respondents, some noted that decision-making has become increasingly complex. The ever-evolving HIV prevention landscape was perceived as creating uncertainty as to the appropriate standard of prevention:

“...the landscape is changing all the time as new data comes in and my impression is that it’s becoming increasingly quite a complicated issue for all the players involved. So in other words I think it’s very difficult for communities to know what to demand as the minimum standard of prevention and I think it’s very difficult for investigators to know what they’re obliged to provide and I think it’s very hard at the moment for ethics committees to know what they should insist as a minimal standard of prevention” (C19, REC).

Reflecting the dynamic and evolving nature of the HIV prevention landscape, respondents’ perspectives on the relevant criteria for the enhancement of the prevention package were varied, as described below.

1.1 Endorsing scientific validity

Most respondents endorsed that new prevention tools should be added to the prevention package when they are scientifically validated (MRC, 2003; UNAIDS/WHO, 2012) and articulated that there should be definitive scientific evidence to support the addition of new tools, for example:

“I think there has to be definitive evidence that these interventions work” (Z16, REC).

1.1.1 Complexities with scientific validity

1.1.1.1 Variable thresholds being used for risk-reduction interventions

The need for clear, definitive evidence advocated by respondents for new interventions was not uniformly applied to all prevention modalities in the current prevention package. While respondents were steadfast in their endorsement of evidenced-based prevention, some conceded that evidence for some of the current tools, e.g., PEP, was not scientifically convincing. This tension between requiring a high standard of evidence for new tools versus making concessions for current tools is aptly captured in the quotes by one respondent below:

“...when we’re talking about state-of-the-art prevention obviously as long as we’re talking about prevention modalities that have been validated, that have been proven...to show effect I have no problems with that” (Z22, site staff, site 1).

“I would still encourage to an extent post-exposure prophylaxis. I mean ehm just ja um like you can see I’m not really convinced [that it is effective] (laughs) but it’s just that you know if it can be made available to participants you know I always encourage them to take that” (Z22, site staff, site 1).

1.1.1.2 Operationalising scientific validity

Respondents’ endorsement of scientific validation was qualified by a degree of uncertainty (e.g., *“It’s hard to really know”*; *“I guess”*) as to when a new tool would be considered scientifically validated:

“It’s really hard to know what the threshold is at which a particular prevention modality becomes obligatory because I think it’s a complex dance between is there enough scientific data to justify efficacy” (C19, REC).

This uncertainty reflected a lack of clarity about how to operationalise scientific validity and interpret complex scientific data, especially for partially efficacious interventions:

“...I think that they [the REC] would consider the available data at the moment [for Tenofovir gel] and be just as confused as every HIV researcher is as to whether it’s effective or not and therefore not include it in the package of care” (C20, REC).

“[The decision to add microbicides and PrEP to the prevention package]... is really a difficult one ...is that data sufficient enough to move that already [to] the standard of care? You know those are the debates that are ongoing but once data is sufficient enough like it came up with the circumcision issue, once we have reached that point then you will have no choice, we’ll have no choice but to make it the standard of care” (Z15, site staff, site 3).

Ethics guidelines only partially facilitate decision-making, and the difficulties suggested with operationalising scientific validity reflect the vagueness of guidelines and the absence of coherent frameworks for decision making:

“...I don’t think at the moment investigators or ethics committees have got any logical tools to help them make firm recommendations...” (C19, REC).

A few respondents attempted to operationalise scientific validity in relation to the effect size, the trial phase, and the number of the clinical trials required before a tool is considered validated. Evidence from one RCT was not considered definitive, for example:

“...so there’s been, you know, a fair bit of push-back...to all the announcements about the gel...because of...the fairly limited effect, and the kind of hype around it,

and people saying, 'Well, we don't even have the right study that we need, and there might be a small effect and dadadada'. (C5, REC).

"And the classical example is that here we had 004 showing some level of efficacy 39% but... VOICE and the daily Tenofovir has shown no effect so it really just emphasises the importance of always confirming a trial before we can move into any policy changes or something like that. And so for 004 it just over emphasizes how critical it is for the FACTS study to go on so we then can compare apples to apples." (Z22, site staff, site 1).

"I guess unless something jumped out so clearly that this is so clearly a big leap forward, and we have to make sure that it's included....my guess is that it would just become part of this gradual, advance, and it would gradually become accepted scientifically, and then it would gradually become accepted at an international level, and then gradually, the government would decide to pay for it, and then gradually we would move towards expecting that as a standard of prevention. Um, so I think it would need to make a dramatic leap forward for us to/ (R: Yes. It would have to be a slam-dunk, and so scientifically convincing for you), right, right, to say like, even if the government doesn't pay for it, you have to do it, because it's just so clearly gonna make a difference." (C5, REC).

1.1.2 Comparing practices and perspectives on scientific validity with ethics recommendations

Ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) set a substantive standard that new HIV risk-reduction methods should be added to the prevention package when they are *scientifically validated* (MRC, 2003, UNAIDS/WHO, 2012, UNAIDS/AVAC, 2011). Scientific validation could be defined as evidence of efficacy of a prevention intervention as demonstrated in a clinical trial (Haire, 2013). However, while guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) establish the standard, they do not define the conditions for scientific validity. Whether scientific validation requires data from one trial, or two, or more is not articulated in guidelines (Haire, 2013, p. 168). Like respondents in this study, some commentators argue that determinations of scientific validity will require consideration of the strength of evidence generated from the efficacy trial, the degree to which results can be extrapolated to other populations and contexts, the conclusiveness of the data, the number of trials that have demonstrated an effect, the need for further confirmatory trials, and the safety profile of the candidate product (van de Wijgert & Jones, 2006; Philpott et al., 2011). Some direction can also be gleaned from regulatory requirements. Regulators, including the South African MCC, typically require that for a new product to be licenced, it should be tested in at least two pivotal phase III efficacy trials (McEnery, 2009; McGrory et al., 2010). However, under

special circumstances, a single pivotal trial (well conducted, well designed and of sufficient size) that provides as much evidence of effectiveness as two trials would have, may suffice (Heise & Wood, 2005; McEnery, 2009). For example, the FDA approved a hepatitis A virus vaccine based on evidence from one phase III trial (McEnery, 2009).

It is asserted that scientific validation is intentionally vague to permit decision-makers the flexibility to make different determinations depending on the particular circumstances (Macklin, 2012). However, data from respondents indicate that it is difficult to operationalise requirements in ethics guidelines because they are so vague. This lack of clarity is also reflected in recent debates in the literature on when to add PrEP to the standard of prevention (Cowan & Macklin, 2014; Dawson, 2012; Haire et al., 2012; Haire et al., 2013). Haire et al. (2012) were critical of delays in the introduction of partially effective HIV prevention products and argued for the relaxation of regulatory requirements in terms of the evidentiary standards for approving and licensing new products. Other commentators (Dawson, 2012) contested that early introduction of tools would be in participants' best interest without sufficient supporting evidence; the need for data from two trials was substantiated by examples of where the first trial showed benefit but additional trials did not, e.g., CAPRISA 004 and the Tenofovir gel arm in the VOICE study. When evidence about an HIV prevention intervention is inconclusive, 'it would be irresponsible for researchers to use these methods as active controls, or for policymakers to roll out the technologies across whole populations, without further research; it is like placing the people at risk of acquiring HIV in an enormous game of Russian roulette' maybe the prevention method is actually effective, maybe it isn't, who knows?' (Dawson, 2012, p. 33) – a perspective with which the present author agrees.

Respondents' comments suggest that there is a need for more logical tools for determining when the scientific validity threshold is satisfied, as echoed by other commentators (Haire et al., 2013; Philpott et al., 2011). The lack of consensus on whether PrEP should be considered standard of prevention in trials is not only reflective of ambiguities about regulatory approval but also of the absence of clear logical frameworks for decision-making (Haire et al., 2013). Some authors have proposed frameworks (Jay et al., n.d.) and criteria (Philpott et al., 2011) for decision-making, which may help expound scientific validity (see Chapter 5). For example, clinical validation considers whether the safety and efficacy of the prevention modality have been established for the trial population; the potential for behavioural factors to mediate this efficacy; the acceptability of the intervention to the trial population; cost and

deliverability; and the potential for interaction effects (Jay et al., n.d.). The pragmatic value of such frameworks for decision-making on the enhancement of the prevention package should be evaluated through piloting.

1.2 Endorsing regulatory approval

Respondents specified that once scientifically validated, there is another threshold for the addition of new tools to the prevention package of regulatory approval and licensure.

It was further specified, primarily by REC respondents, that the intervention would need to be approved by the national regulatory authority in the host country before it could be provided to HVT participants:

“...now there’s FDA approval of Truvada as a prevention modality and then there’s the issue of even if it’s FDA approved is it feasible to provide it locally um [if] it’s not yet approved by our own regulator as a prevention modality...” (C19, REC).

“...the regulatory authority in that country, basically registering those interventions...” (Z12, REC).

R: ...would it be quite important that a new methodology had been approved ... by our own national authorities so it became part of our standard of prevention before it should be provided to participants?

C21: I think that answer is an affirmative yes. (C21, REC)

1.2.1 Comparing practices and perspectives on regulatory approval with ethics recommendations

Ethics guidelines recommend that new HIV prevention methods should be added to the standard of prevention based on *approval* by relevant authorities (UNAIDS/WHO, 2012) or national bodies for use (UNAIDS/AVAC, 2011). The approval requirement is recommended as an alternative to scientific validation by UNAIDS/WHO (2012) guidelines and to augment scientific validation by GPP guidelines (UNAIDS/AVAC, 2011).

The recommendation for approval by relevant authorities is problematic because different regulatory and normative bodies use different criteria for approving prevention interventions (McGrory et al., 2010). Further, UNAIDS/WHO (2012) guidelines are unclear on whether approval would be required by the national regulatory authority, or whether any regulatory or normative body approval would suffice (Haire, 2013). GPP guidelines however, stipulate

national approval as a prerequisite for new tools to be added to the prevention package (UNAIDS/AVAC, 2011) (see Chapter 11 for detailed discussion).

1.3 Stakeholder consultation

UNAIDS/WHO (2012) guidelines also contain a procedural requirement for the enhancement of the standard of prevention which specifies that new HIV risk-reduction methods should be added to the prevention package based on *consultation* among all research stakeholders, including the community. Such consultations should consider (1) feasibility, (2) expected impact, and (3) the ability to isolate the efficacy of the biomedical HIV modality being tested (UNAIDS/WHO, 2012). Respondents in this study did not spontaneously endorse consultation with relevant stakeholders as a criterion for the enhancement of the prevention package. In a companion study that quantitatively explored perceptions of care and prevention norms in ethics guidelines (Moorhouse et al., 2014), respondents reported low agreement with the recommendation that new prevention methods should be added to the prevention package based on consultation with all stakeholders. This recommendation was also rated as problematic in terms of ease of implementation, ease of understanding and the degree to which it protected participants (Moorhouse et al., 2014).

Respondents' perspectives on the value of stakeholder consultation in standard of prevention determinations, is detailed in Chapter 10 which considers respondents' perspectives on ethics guidelines.

1.4 Additional criteria

In addition to the ethics guideline requirements of scientific validation and regulatory approval, respondents identified additional criteria for consideration when making decisions about the enhancement of the prevention package, namely, availability in the public healthcare sector and the phase of the trial.

1.4.1 Availability in the public healthcare sector

Some respondents, particularly REC members, identified public sector availability as an additional criterion for consideration, that is, the new intervention should be available in the public healthcare sector before it is offered to participants in HVTs. In this way, respondents advocated for a localised standard of prevention:

“...it’s always got to be seen in relation to whatever the local standard of care is and ...my perception is that the national/the local standard of care is the one that prevails in local ethics committee determinations.” (C19, REC).

“I think the interventions have to be part of public sector practice. That is, if the government decides that for instance...they’re not going to make PrEP available in the public sector, I think then it would be hard to justify requiring it from a local ethics committee.” (Z16, REC).

“I think, number one, confirmatory results. Number two, preferably implementation trial results, and, I think, number three, obviously, the regulatory authority in that country (.) basically registering those interventions, or changing the indication of those interventions from treatment, to treatment and prevention. And I think when those three things, and when the intervention becomes available in the public sector, all four of those conditions then would pave the way for that to be offered to trial participants.” (Z12, REC).

“Now, and I think we should work towards whatever is being suggested as the state-of-the-art prevention package should really form part of, part of the standard of care which is available in the public services” (Z15, site staff, site 3).

Some respondents justified their endorsement of public sector availability as related to concerns about sustainable access to prevention interventions post-trial, for example:

“And the other question is that, should that site actually be a trial site at all if, once the study ends it’s not going to continue, or there’s no availability in the public sector.” (Z12, REC).

“I think it’s because research has a limit. There’s a duration of time. We are doing research for the 3 years. If you’re providing more services that is not in the public sector where is the participant going to get that because when they were exited they have to refer back to...their public health sectors.” (Z2, site staff, site 1).

“Sustainability is one of the things that we consider...we haven’t had to consider it as carefully up until now because of the availability of syndromic management, the availability of circumcision, but that will definitely be part of the discussion...when we’re considering our next big trial” (Z9, network representative).

However, it was noted that some tools (e.g., PrEP) do not raise such sustainability concerns:

“PrEP is a little bit different from therapy in that someone can benefit from PrEP over a certain period of time and not access it again but still have that benefit for that period of time without” (Z16, REC).

While REC respondents unequivocally endorsed public sector access as a pre-requisite for inclusion in the prevention package, some site staff were of the view that accessibility in the public sector would not always be a determining factor, granted that sponsors *“are prepared to fund”* the intervention (Z7, site staff, site 1).

1.4.1.1 Complexities with public sector access

1.4.1.1.1 The politics of policy development

Despite strong advocacy for a localised standard of prevention accessible in the public healthcare sector, it was acknowledged that the public sector might sometimes lag behind in introducing new prevention technologies. Particularly in South Africa, some respondents seemed weary of poor government policy decisions regarding HIV, given the history of AIDS denialism during former President Mbeki's tenure (Jones, 2005; Patterson & Cole, 2006). For example: “...if the government is a stakeholder, and we were in the Mbeki era, we would be in big trouble” (C4, site staff, site 2) and “...that's our government, they take time to deliver things” (J1, site staff, site 2).

Therefore, relying on public sector access as a benchmark for the standard of prevention in HVTs could result in unnecessary delays on political grounds, as was the case with PMTCT (Dawson et al., 2014; Philpott et al., 2011). Similarly, despite VMMC being proven effective in three RCTs, rollout of this intervention in the South African public healthcare sector, was slow (Bateman, 2010). While UNAIDS/WHO recommended VMMC as an additional HIV prevention methodology in 2007, the South African national circumcision policy document was only launched in 2011 (cf. Mayosi et al., 2012).

1.4.1.1.2 Disjuncture between national standards and local realities

While public healthcare policy is often established at a national level, realities experienced at public healthcare facilities may differ. These differences are experienced both between and within facilities in various South African provinces (cf. Stuckler et al., 2011). Some respondents reported that variable access to prevention interventions was a characteristic of the South African public healthcare sector. For example:

“...the standard of care means different things to different people even if you're looking just within the health system of one country. The standard of care in Cape Town is different than in Durban or Bloemfontein...it's an interesting question to me, conceptually, to think about, do we owe them standard of care in Cape Town, or if they're from the Eastern Cape, do we owe them that standard of care?” (C5, REC).

“I mean I think it comes down to, what's the standard of prevention? And (.) obviously the clinical trial has to take that into consideration. Um, and that in itself is quite a vexed question, so, what are we going to make the standard of prevention, countrywide? And, what is going to be the standard of prevention for our research

protocols? Um, and is that going to be community-specific? Or is that going to be country-specific? Or is that going to be protocol-specific?” (Z18, site staff, site 5).

“...in many areas of South Africa, from what I understand, access to treatment for HIV-infected individuals can still be problematic in some areas. And (.) so, access to PEP or PrEP for prevention of HIV infection, while a laudable goal, may not be practical in South Africa...” (Z9, network representative).

Two different dimensions of accessibility were distinguished, namely theoretical access (standard of prevention as in guidelines) and actual access (standard of prevention as in practice). It was suggested that “actual access” may not be a pre-requisite but that theoretical access was the actual determinant:

“...you also have theoretical access versus actual access, so you qualify for it, but then there’s a long waiting list, or you qualify for it but it’s not being provided in your area. So it’s the standard of care in the country, but when you go to a district, or even, a particular city level, it’s not available in that particular study, or that host community” (Z12, REC).

“...the two things that come up in the discussions often that are kind of points of contention, um, is one, when we mean ‘standard of care’, do we mean, what’s written down in the guidelines, or what actually happens in the...public health service.” (C5, REC).

A contrary view was that the standard of prevention implemented in trials should be determined by actual availability in the particular context, rather than by the established national standard. If actual access was not available in a particular context, then the prevention intervention should not be added to the prevention package:

“I think that it’s true, they [participants] should be provided with everything but then you also have to look at the context of uh you know your settings. I mean they could have told us that we need to provide male medical circumcision but then if/ just say that our research site was in the Transkei or something, and there’s no medical doctor there to actually provide the service...So in that case the nearest referral would be Durban and then we would still refer them to Durban but if there’s nothing available on-site or locally, then we wouldn’t be able to provide that service” (Z7, site staff, site 1).

1.4.1.2 Comparing practices and perspectives on public sector availability with ethics recommendations

The criterion of public sector availability, endorsed by some respondents in this study, is not a requirement of MRC (2003) and UNAIDS/WHO (2012) guidelines. While GPP guidelines (UNAIDS/AVAC, 2011) suggest that research teams and relevant stakeholders consider the current standard of prevention available nationally and locally when discussing and

negotiating the HIV prevention package, they do not suggest that public sector availability should be the benchmark for the standard of prevention. Respondents' views concurred with network-specific guidelines developed by the HPTN (2009) that the standard of prevention should be practically achievable, reasonably accessible, and locally sustainable. Similarly, respondents justified their endorsement of public sector availability based on ensuring sustainability of the standard of prevention post-trial. Concerns that new prevention interventions should not be added to the prevention package if they are not sustainable in the trial setting after the completion of the trial, is a sentiment supported by others (McGrory et al., 2010). Further, the strong endorsement by RECs in this study that new tools should be nationally approved and available corresponded with perspectives of RECs reported at the Ugandan consultation (McGrory et al., 2010). Respondents in an empirical exploration (Haire & Jordens, 2013) also suggested that implementing enhanced prevention services that cannot be sustained post-trial is ethically problematic. However, a competing view is that as long as the feasibility of the trial is not undermined by the addition of the new prevention modality it can be argued that the immediate potential benefit of reduced HIV infection risk for study participants is a legitimate derivable benefit from the trial for the community, even if this cannot be sustained beyond the research (Haire et al., 2013, p. 7).

1.4.2 Phase of the trial

Some respondents articulated different obligations to participants enrolled in different trial phases because participants' risk of HIV infection differs. Trial participants in early-phase trials are at lower risk of HIV than participants in late-phase trials. If the ethical principles of beneficence and non-maleficence are considered, then it seems reasonable that participants' risks of acquiring HIV should be offset by the provision of proven HIV prevention modalities so the higher the risk, the better the standard of prevention:

"...it obviously depends on the phase of the trial. It's safe to say one or two you can't do too much prevention. Phase three obviously becomes more difficult to show efficacy of the product if you have that many prevention strategies in place but I think it's still our moral duty to do that even if it makes the study more difficult to do" (Z17, site staff, site 5).

"...because it's a lower-risk protocol, the imperative to make sure it was in place was probably lower but it just happened that we were setting up those services anyway so we're in a situation where people can access them if they want them." (Z6, site staff, site 2).

“Well, I can tell you that for the largest trial that we’ve done so far in South Africa, we offered circumcision. We’ve done a couple of low-risk trials since then, which, we weren’t able to offer circumcision as part of this...” (Z9, network representative).

In the drafting of protocols, it appears that the phase of the trial influenced the standard of prevention. The phase IIB protocol specified risk-reduction counselling, male and female condoms, STI treatment, and access to PEP and VMMC while the phase I protocol only specified that risk-reduction counselling would be provided.

An alternative view was that participants are owed the same standard of prevention regardless of the phase of the trial, because the risk of HIV infection is not only a function of participant behaviour but may also be related to the vaccine product. It was acknowledged that participants in early-phase trials may have lower uptake of prevention services, but that these should be consistently offered to participants in all trial phases.

“They should be provided with a high standard of care regardless of what phase they’re in, because the risks are basically the same. Because remember with...the adeno-5 vaccine that ended up causing people, or, possibly increasing the risk of them acquiring HIV. So, at the end of the day it didn’t matter if they were getting that vaccine in the context of a phase II or in the context of a phase III, the point is that they were getting that vaccine... it’s not necessarily a case of the higher the phase of trial, the more, or the better your standard of care should be, you should have standard of care from, whatever the, level of intervention is” (Z12, REC).

“I think you know we still offer all of the same care and prevention methods. Maybe there’s less uptake within those groups.” (Z13, network representative).

1.4.2.1 Comparing practices and perspectives on the trial phase with ethics recommendations

Ethics guidelines do not specify whether the obligation to provide prevention services differs according to the phase of the trial or risk-level of participants. However, UNAIDS/WHO (2012) guidelines mention in the guidance point on clinical trial phases that different trial phases present different scientific and ethical requirements. Some commentators (Slack et al., 2000) have also hinted at this distinction by suggesting that since participants in efficacy trials are enrolled because they are at high-risk of infection, the principle of beneficence obligates researchers to reduce harm. Similarly, data from this study indicated that protocol-writers accorded different obligations to early-phase and late-phase trial participants, a practice endorsed by some respondents in this study. However, consideration of participants’ susceptibility to risk may not accurately acknowledge context-specific and structural-level

risks, given that a woman in Kwa-Zulu Natal in South Africa, for example, faces a 25% lifetime risk of HIV acquisition, while an Australian woman's risk is less than one-thousandth of that (Haire et al., 2012, p. 28).

1.5 Adding VMMC to the prevention package

At the time of data collection, VMMC was the only new HIV risk-reduction intervention deliberately added to the prevention package. Respondents who were privy to the decision-making process described the relevant criteria considered and the stakeholders involved in the decision to add VMMC to the prevention package.

VMMC was reportedly added to the prevention package based on clinical trial findings that it significantly reduced male risk of contracting HIV during heterosexual sex (Auvert et al., 2005), for example:

“...at the time we were doing protocol development for that, which was, November 2005 I think...there were two trials. I can't remember what the order was but there was...the circumcision trial from Kenya and the circumcision trial from Orange Farm in South Africa. One had been published and one hadn't. So there was some debate about it but I think a lot of people knew the results of the second trial anyway, even though it hadn't been published yet. So, we knew that this was coming, and we also knew that the protocol development process was going to take some time before it was approved, so we knew...by the time the protocol was final, we were likely to have circumcision as another prevention tool, in our toolkit.” (Z9, network representative).

The initial decision to provide VMMC to trial participants based on the results of the South African trial was strengthened by the results of two additional trials (Bailey et al., 2007; Gray et al., 2007) which became available before the phase IIB trial commenced at sites (Essack, Slack, et al., 2010):

“Yeah so that [the decision to add VMMC] was driven by three studies and an increasing international acceptance of circumcision...so I think by the time it was included in the package of prevention care it was already becoming acceptable. So the WHO already had their meetings, they may not have released their documentation but they'd already had their meetings.” (C20, REC).

Many respondents supported the offer of VMMC to participants based on the *“overwhelming scientific evidence that it works”* (Z7, site staff, site 1). In conjunction with ethics requirements to offer *“all the available resources”* (Z11, site staff, site 2) to participants, it was noted that withholding proven interventions was not justifiable.

Respondents reflected that despite the evidence of efficacy, there were objections to the rollout of VMMC in South Africa:

“...one of the persons who was against the rollout of the circumcision, disappointingly so, is an advocate, who is key in HIV research...there was a lot of ongoing, you know, backwards and forwards, and with some people for it, and some people just not supporting” (Z11, site staff, site 2).

Conflicting perspectives on VMMC were noted to have impeded rollout of the provision of VMMC to participants *sans* accompanying scale-up in the public healthcare system was argued as “*beyond the standard of care*” (Z22, site staff, site 1). However, it was reported that given knowledge of the protective benefit of VMMC and that participation in HVTs is a voluntary endeavour, participants should be offered “*the best care that is affordable*” (Z22, site staff, site 1). Some ethicists have argued that researchers are not obligated to provide VMMC until it has become an established and accepted prevention intervention within the larger community. It can, however, be offered to participants when researchers can afford to do so (McGrory et al., 2010).

As with overall standard of prevention determinations, the addition of VMMC was largely determined by the protocol committee (including representatives from the sponsor, network, local investigators, and CABs) during the protocol development stage (see Chapter 7). The inclusion of VMMC in the prevention package was reviewed and formally approved by all RECs with jurisdiction over trial sites as well as selected CAB representatives, and required the formal approval of all relevant RECs. The product developer, as the financier of VMMC in the phase IIB trial, was also a critical stakeholder in the decision to add VMMC. Respondents also reported informal discussions with government stakeholders.

1.5.1 Complexities with adding VMMC to the prevention package

1.5.1.1 Cultural implications of providing VMMC

While adding VMMC based on scientific evidence was considered a sound medical decision, there was some concern that the cultural implications had not been as carefully considered. Given that not all sites and CABs were engaged in protocol development and review (see Chapter 7), the lack of widespread community consultation on VMMC was perceived by some as a challenge because of the related cultural ramifications. At one site, it was reported that some CAB members objected to the provision of VMMC as it “deviated” from their

cultural practices. Again, the perception that the CAB had limited ability to change things was reported:

“...some of the CAB members they do oppose the circumcision which is provided by the site because they said now we are deviating from the cultural norms because the [name of ethnic group] are not doing the circumcision. So meaning that if we are taking the participants for the circumcision, we have to inform the extended families so that they can do some ceremonies, all those things. What if they are coming from the poor background and they are not prepared to do those things? It was their [the CABs] concern but nothing was done about it because the participant were circumcised, they are the one who made the decision not their families.” (Z2, site staff, site 1).

Nevertheless, a lack of cultural acceptability did not always translate into poor uptake by participants. At the site where some CAB respondents opposed the provision of circumcision, uptake of VMMC was reportedly high (see Chapter 9).

1.5.1.2 Lack of REC input

In reflecting on the decision to add VMMC to the prevention package, RECs were portrayed as having adopted a passive role in decision-making, for example:

R: To your knowledge was the REC involved in discussions with the researchers when male circumcision was added to the prevention package?
Z16: Not to my knowledge, no. (Z16, REC).

“It was pretty much a discussion between the people implementing or preparing to implement the specific study in the site. The REC wasn’t really making any pronouncements or advocating for any particular position...but as a whole they’re not activists in the sense that you know I’ve yet to see them say you know ‘we think that your standard of care should include X’” (Z6, site staff, site 2).

Rather than being intricately involved in the decision-making process, the role of RECs was perceived as limited to approval of the addition of VMMC to the prevention package.

It was also reported that some REC members may not support the provision of VMMC because they have doubts about its efficacy:

“I know that there are members on [the REC] who are very much against medical male circumcision. They’ve taken a very strong line against it.” (Z12, REC).

Importantly, unlike with provider beliefs of efficacy, REC perceptions on the efficacy of VMMC did not result in their disapproval of the prevention package. Rather, it was reported that RECs undertook to ensure that information on the risks and benefits of VMMC were

clearly outlined to participants. While such risks were not specified in ICFs, it was reported that participants were counselled on the risks and benefits of circumcision.

1.5.2 Comparison of decision-making practices and perspectives with ethics guideline recommendations

In line with the substantive requirement for scientific validity (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) which was also endorsed by respondents in this study, VMMC was added to the prevention package based on evidence of efficacy. However, VMMC was added to the package before its endorsement for use by national or international bodies (Haire et al., 2013) such as the WHO. In contrast, other empirical studies found that VMMC was only added to the prevention package of other HIV prevention trials after national guidelines were developed (Haire & Jordens, 2013; Ngongo, Priddy, et al., 2012). Such differences in approach may reflect ambiguities between companion guidelines, with one set of guidelines (UNAIDS/AVAC, 2011) advocating for both scientific validation and national approval and the other (UNAIDS/WHO, 2012) allowing for either condition.

Insofar as the decision to add VMMC occurred during protocol development (which included select CAB representatives) and was reviewed by some CAB members and all relevant RECs, the procedural requirement for consultation among all research stakeholders, including the community (UNAIDS/WHO, 2012) was somewhat satisfied. However, guidelines do not prescribe the process for consultation. Structured decision-making processes (e.g., Tarantola et al., 2007) have been advocated for making determinations on the standard of prevention (Hankins et al., 2009; Philpott et al., 2011) but were not reported in decision-making regarding the addition of VMMC.

While some respondents in this study supported the view that new prevention methods should only be provided to participants when they are available and accessible in the public healthcare sector, VMMC was offered to phase IIB trial participants at a time of limited accessibility in the public sector (de Bruyn et al., 2007). This practice appears to be in agreement with the three-step framework, which is explicit that new prevention tools should not be incorporated into the prevention package too late, that is, only after introduction in local healthcare systems (Jay et al., n.d.). Further, once a new prevention tool is considered validated, its addition to the prevention package should not be contingent on regulatory

approvals as long as it is considered appropriate and can be sustainably implemented in the local healthcare system (Jay et al., n.d.).

The inclusion of VMMC in the phase IIB study protocol and not in the phase I protocol, underlines some respondent arguments that the phase of the trial is a critical consideration for standard of prevention determinations.

2. Challenges with evolving standards of prevention

2.1 Adding new tools may impact on trial feasibility

The concern that adding new modalities to the prevention package will reduce HIV incidence was acknowledged in the phase IIB protocol “although the HIV seroincidence in South Africa has been estimated to be more than 4% in most of these settings, for the purposes of this study we have assumed that the HIV infection rate will be reduced due to enhanced prevention activities” (p. 13). Such decreases in incidence may imperil the ability of the trial to generate meaningful results (Padian et al., 2010).

Most respondents recognised that as new modalities are added to the prevention package, it may become increasingly difficult to conduct HVTs:

“...the irony is that it masks... the efficacy of a vaccine, you now potentially have other confounding factors that could be preventing HIV, if you take the current, or emerging standards of care. So now for example we have medical male circumcision, we have the issue of HIV drugs as prevention, we have microbicides, and if those become standard of care then you have all those potential interventions also as confounding factors or possible prevention blockages to HIV, rather than just the vaccine...” (Z12, REC).

“...it’s the Nancy Padian golden egg paper of 2010...if we reduce the incidence so markedly, we will not be able to tell the difference between products because of just creating, such a logistical difficulty. In other words, to power the study sufficiently to show a difference in your product and non-product, or strategy and no strategy means that the study will have to be so big, that it just becomes logistically impossible. And so the concern, is that, by increasing and increasing our standard of prevention, you make a population who, just have no chance of HIV acquisition, and therefore you reduce transmission to such an extent” (Z18, site staff, site 5).

It was argued that given the potential to impact on the scientific validity of the trial, careful consideration should be given to the enhancement of the prevention package:

“...to just willy nilly put in new things all the time will destroy the value of the study that’s going on” (C17, REC).

Respondents agreed that concerns about trial feasibility were real, but some suggested that the potential impact has been somewhat inflated. Many respondents framed their discussions of feasibility as a tension between ensuring the scientific integrity of the trial and the need to ensure the welfare of trial participants, with most arguing in favour of protecting participants. Scientific integrity or the ability of the trial to generate meaningful results was noted as related to sample size ó respondents implied that increasing sample sizes to ensure an adequately powered trial, although costly and demanding in terms of participant accrual, was a necessary evil:

“I think that [trial feasibility] is a real concern and it’s one that we should learn to live with...the suggestion or the possible idea that we should be denying participants prevention interventions in order to observe a higher HIV incidence is obviously untenable. So I think it’s a real concern but I think it’s, it’s a fact and it’s a fact that we need to account for and adjust for. ...I think the conflict is a little bit inflated by people and is a little bit less dramatic than some people think” (Z16, REC).

“...of course that makes it harder to find a difference, because if you’re effective in your other forms of prevention, the lower the rate of infection, and you’re gonna need more people in order to see a difference in terms of the design and I think that’s a perfectly reasonable trade-off” (C5, REC).

“...if it means increasing your numbers, then you’ll have to increase your numbers in the trial but I don’t think you can really not provide HIV prevention options for participants” (Z7, site staff, site 1).

Enrolling large sample sizes is possible ó the success of the Thai RV144 trial was not only that it was the first HVT to demonstrate proof of concept, but also that it enrolled over 16000 participants and retained over 90% in a six-year period. Nevertheless, the inclusion of PrEP in the prevention package of HVTs would complicate trial design. Typically, HIV incidence rates of 3-6% have been found among trial populations in efficacy trials, and these may decrease further with the addition of effective HIV prevention strategies. Relatively low incidences limit the ability of detecting moderate efficacy in trials (Reynell & Trkola, 2012). For example, if a microbicide (e.g., CAPRISA 004) or product of similar efficacy is added to the standard of prevention, the incidence of HIV infection would decrease by at least 30-50% - òa trial such as RV144, which followed 16,402 participants for 3.5 years and detected only 125 infections, would be under-powered to retrieve data for outcome analysisö (Reynell & Trkola, 2012, p. 5).

Withholding a scientifically validated prevention modality from participants solely to ease the burden of increased sample size and resultant expense was argued to be ethically abhorrent and likened to the infamous Tuskegee study:

“...the one thing that is obvious is that as more and more prevention modalities become available and form the prevention package, obviously for ethical reasons you’ve got to provide that to participants...The one thing that we’re gonna have to live with is that then it just means our trials are gonna get more and more expensive because we/ it therefore means we need to have bigger and bigger numbers to reach the endpoint that we’re looking for....as we advance in science...we gonna be getting more prevention modalities and we can’t then now deny/ otherwise we gonna end up with the Tuskegee trial situation where we want to say we gonna withhold this because otherwise we can’t achieve what we want to achieve in trials. And we can’t allow that to happen.” (Z22, site staff, site 1).

Network representatives confirmed that the addition of PrEP to the prevention package would indeed amplify costs because of increased sample sizes but that this would not translate to withholding PrEP from participants:

“... ART as PrEP that also may come to be something that we need to offer in our trials. In which case we’re going to have to enrol like three times as many people as we thought (laughs)...It will get very interesting but if it’s the right thing to do, we should do it.” (C13, network representative).

“...I think it can impact on the feasibility. Sure uhm but I don’t think that’s a reason you know not to try and implement a full standard of prevention package and I do think/ I think at least the researchers that I’m aware of within [the network] work very hard to make sure that it’s done in a way that is feasible so the prevention packages can be included.” (Z13, network representative)

A common view held by respondents was that regardless of logistical complexity and costs, “we aren’t going to peel things off” the standard of prevention (Z6, site staff, site 2).

However, in a different study, some interviewees argued that there should be efforts to concentrate on the experimental product and “peel back from offering everything” (Haire & Jordens, 2013, p. 11). In contrast, none of the respondents in this study explicitly supported the latter view, although a few argued that enhanced prevention packages might severely cloud the effect of an experimental vaccine and might result in trial futility, for example:

“Well I mean we’ve already seen some ongoing studies being abandoned because the incidence of HIV in those studies was seen to be too low. So that’s the sort of thing where if it comes to an end, that’s a dead end and the information that we learn from that study is very limited” (Z6, site staff, site 2).

Standards of prevention are based on the tenet that the researcher’s principal obligation is to reduce participants’ risk and prioritise their well-being over considerations of future

beneficiaries of research (Haire et al., 2012). Decision-making criteria (Philpott et al., 2011) and frameworks (Jay et al., n.d.) specify that when making determinations on adding tools to the prevention package, the impact on trial feasibility should be considered. A new prevention tool should not be added to the prevention package when it is so effective that showing an added effect from the study intervention will require a sample size and/or duration that is substantially misaligned with a reasonable allocation of resources (Jay et al., n.d.). For example, treatment as prevention has been found to be 96% effective in reducing HIV acquisition in serodiscordant couples (Cohen, 2011) and would likely dramatically reduce HIV incidence if provided to trial participants. Such an effective prevention intervention would require trials of significantly increased sample sizes to have sufficient power, at a level unlikely to be feasible (Haire, 2014). For this reason, future HIV prevention trials will be unlikely to recruit participants in serodiscordant relationships (Haire, 2014).

Still, some respondents in this study considered providing sub-optimal prevention packages to ensure sufficient endpoints, untenable ó rather one proposed solution was to conduct research with those populations who fail to implement current prevention interventions:

“...by making those provisions available to people, doesn’t mean that those people are going to take them...unless you force it down their throats...this is still going to come down to human behaviour. So, it may be, that in the future, we need to think of ways where we would enrol people who genuinely don’t want to use those strategies, or, we know that, even if we make them available to them, they won’t use those strategies...sadly in my own site, where I think we do excellent risk-reduction counselling, condoms are always available, I treat anybody who presents with an STI, I often test those people who ask for it, I still had an extraordinary incidence in that population. So, you know, I think, whilst that is a consideration, and there may come a time when we just put ourselves out of business because we cannot do efficacy studies, because the whole population is just preventing so well, well then, you know, then I’m hoping the HIV epidemic will be coming under control, and we will be, you know, not needing anything more going forward. The fact of the matter is that I think, around the world, there are lots of pockets of transmission going on, and we’re just going to have to find those pockets, and use those in our clinical trials going for/ I think it will get harder, because I think they’re gonna be more difficult populations to reach, they’re gonna be more difficult populations to inform, and to provide services for, but, you know, I think that’s the natural history of this thing. Um, I, honestly, at this stage, don’t believe that we can entertain for a moment that we would do some less standard of prevention, in order to conduct an efficacy study” (Z18, site staff, site 5).

2.2 Adding new tools is costly

Implementing enhanced standards of prevention has implications for the costs of clinical trials because larger sample sizes, and therefore exponentially more funding, will be required

to meet study endpoints (Haire et al., 2012). This is further compounded by increasing research costs as a result of routine inflationary increases of all occurring in a context where research funding is stagnating (RTWG, 2013; 2014).

A network respondent noted that funding may well be a consideration for standard of prevention determinations: *“I think you know expense may sometimes come into the picture. I certainly hope that that’s not something that interferes though”* (Z13, network representative). The reality, as described by many respondents, was that funding was a major determinant of standard of prevention decision-making, especially considering donor restrictions of funding. For example:

“And we’ve also discussed to what extent would these resources be applied to other prevention modalities...that it could be very costly...Truvada, oral PrEP, microbicides these are not typically interventions that [the sponsor] would pay for under study protocol costs, right? So you know that may be an issue in the future as some of these other interventions become the standard of care, yeah.” (C14, network representative).

“...it’s a funding issue...the largest trial that we conducted... [the product developer] actually provided the funding for the circumcision procedures, so those were not government dollars. The other trials that we’ve been doing have been... funded by the US government, but they’ve been South African products. And there just wasn’t money available for them.” (Z9, network representative).

“So the least that we can do is to offer them the best that we can...obviously within financial constraints...” (Z22, site staff, site 1).

“...there’s always been a bit of a discussion on things around you know what they can afford or what not. Especially because there’s always a financial issue... You know sites insisted on having a list of things available for their participants and you know the sponsors not being willing to provide it because then it would include a much bigger cost component to the protocol.” (Z17, site staff, site 5).

2.3 Adding new tools may be an undue inducement to participate in HVTs

Several respondents were concerned that the addition of new prevention interventions not otherwise available or affordable would constitute an undue inducement to participate in the HVT:

“I think that’s going to be problematic because then we’re doing something that’s not standard of care and I would be worried about the reasons why people would then take part in the study. Because it might be purely just because they want to access that. Ja no I won’t, I think it would be problematic if you add something that’s not otherwise available.” (Z17, site staff, site 5).

“I don’t think it’s fair. The only concern for me it’s mentioned that participation is voluntary. Now if you put such things there I don’t know whether I should say it but you know it entices people that if you come here you are going to get this and this. It doesn’t sound nice. It seems you are bribing people, you are telling people that now if you take part in this you are going to get this and this... For a study to be credible, people should not be bought to take part in it, but if you bribe people to come and take part the credibility of the study reduces.” (C12, CAB).

“...should we be providing an extra package just for participants and then there would also be the, which is still really a debate the question of when we’re doing that isn’t that a conducive incentive? You know because then you know here you are for participants you’re providing what they otherwise would not have received” (Z22, site staff, site 1).

“I think that’s always a big concern is if they’re not available to the public are we offering an undue inducement to participate in the trial you know by providing them.” (Z13, network representative).

Like these respondents, HPTN (2009) guidelines argue that offering a state-of-the-art prevention package, when such interventions are unavailable in the community, may create an undue inducement to participate. Concerns about undue inducement in research are not new (see Chapter 5), and some assert that this ethical concern has been over used or misused in discussions of trial ethics (McGrory et al., 2010, p. 29).

2.4 Adding new tools may create inequities between trial participants and their communities

Some respondents in this study were of the view that the evolving standard of prevention should be determined by the availability of the particular intervention in the public health sector.

For a few respondents, there was concern that adding new tools, not otherwise available, to the standard of prevention would create inequities between trial participants and host communities. In this way, these respondents adopted a social justice perspective, which argues that the standard of prevention implemented in HVTs should not be so superior in comparison to the standard of prevention in the community that it could not be feasibly and timeously integrated into the local healthcare sector on completion of the trial (HPTN, 2009). Requiring that all new and validated tools be provided to participants in HVTs when they are otherwise unavailable or unaffordable would create serious inequities between research participants and community members with similar needs (HPTN, 2009, p. 33). Given the potential for social injustice some respondents argued that “...long-term there should be a

move towards having these available to all our...patients regardless of their participation” (Z15, site staff, site 3).

While other respondents did not necessarily support this perspective, there was some acknowledgement that it could be a potential complexity:

“Because, you know, if something is not a standard of prevention in the country, and then it’s offered in a clinical trial, that could well have implications for that community, you know” (Z18, site staff, site 5).

Still other respondents supported a reciprocal justice perspective (see Chapter 7), that trial participants are deserving of special treatment in the form of access to services or benefits not available to others, because of the risks they are exposed to.

2.5 New tools may replace the old

A concern for some respondents was that as new partially effective prevention modalities become part of the prevention package, participants may be less likely to use previously available prevention strategies like condoms:

“I think the challenge, is that when you introduce a new prevention method, the person thinks that ‘ok, I can get rid of what has been existing’...they’re thinking that the new methods that have been introduced are there to substitute the others” (Z2, site staff, site 1).

“...[if microbicides are added to the prevention package] it will change the whole thing...People are going to minus the condom part and use the gel.” (J1, site staff, site 2).

It was emphasised that clear counselling messages on the importance of condom use, despite the availability of new efficacious products, should be imparted to participants. For example:

“... it would also go with a lot of education for the community and the study participants because they would obviously need to understand very clearly that if they do get a microbicide added to a vaccine trial and the microbicide efficacy was shown to be say 63%...it’s not 100% effective...don’t think because you’re using microbicide you won’t get HIV infection. Still use your condoms, still you know practice safe sex you know all those things they need to understand...” (Z17, site staff, site 5).

Given that an HIV prevention modality with full efficacy is unlikely, participants should be counselled on the value of combination prevention strategies.

3. Summary

This chapter addressed the research question on what are the perspectives and practices of HVT stakeholders on evolving standards of prevention. Ethics guidelines specify two substantive standards for the addition of new HIV prevention interventions to the prevention package. Firstly such interventions should be scientifically validated (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Secondly, they should be approved by regulatory authorities (UNAIDS/WHO, 2012) or national bodies for use (UNAIDS/AVAC, 2011). UNAIDS/WHO (2012) also specifies that new tools should be added based on consultation among all research stakeholders, including the community.

Respondents largely agreed with ethics guideline recommendations that new tools should be added when they are scientifically validated, although the operationalisation of scientific validity was identified as a complexity, particularly considering that guidelines are vague. Scientific validity was also reported as the basis of the decision to add VMMC to the prevention package. The need for clearer operational frameworks for researchers, RECs and regulatory authorities was also identified.

In line with UNAIDS/AVAC (2011) guidelines and a more stringent interpretation of UNAIDS/WHO (2012) guidelines, respondents reported that a new prevention modality would need approval of the national regulatory authority in the host country before it is offered to HVT participants.

Public sector availability and the phase of the trial were also articulated as relevant to determinations on the enhancement of the standard of prevention. Neither of these criteria are explicitly spelled out in ethics guidelines. Data from this study support the perspective that researchers should provide participants with proven, nationally approved and available prevention methods (McGrory et al., 2010).

CHAPTER 9

STANDARD OF PREVENTION IMPLEMENTATION PRACTICES AND PERSPECTIVES

This chapter presents respondents' reports on the HIV prevention interventions provided in two HVTs at five South African sites. It describes which prevention interventions were provided, to whom (participants, volunteers at screening, participants' partners or the wider community) and how (implementation practices). Respondent perspectives on standard of prevention challenges and complexities are also presented. HIV prevention practices at sites are compared with relevant HIV prevention recommendations in ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Findings in this chapter were published in *Public Health Ethics* (Essack, 2014).

1. Which HIV prevention interventions were ensured in HVTs?

An analysis of site documents and interviews revealed that risk-reduction counselling, male and female condoms, STI treatment, VMMC and PEP (where indicated), were provided at the five South African HVT sites.

Implementation practices and complexities are presented below according to each prevention intervention for trial participants and then for non-trial participants.

1.1 Ensuring access to risk-reduction counselling

There is broad consensus from multiple stakeholders that participants in HIV prevention trials should be provided with behavioural risk-reduction counselling (Lagakos & Gable, 2008). While some behavioural risk-reduction interventions have been proven effective in reducing self-reported risk behaviours and even STIs, to date there is no evidence showing significant reduction in HIV infections (Lagakos & Gable, 2008; Lie et al., 2006). However, risk-reduction counselling is invaluable for enhancing knowledge of HIV/STIs, enhancing skills for condom use and increasing the effectiveness of biomedical interventions (Heise et al., 2008; Lagakos & Gable, 2008).

Ethics guidelines recommend that trial participants should be provided with risk-reduction counselling (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Both study

protocols and interviews at all five sites, indicated that on-site risk-reduction counselling was provided to participants at every study visit. Risk-reduction counselling was reported to be *in-depth*, taking *plus-minus 30 to 45 minutes* (Z4, site staff, site 2) up to two hours to complete, depending on individual participant needs. Given that phase I trial participants were at lower risk compared to those in the phase IIB trial, it was reported that the length and *“nature of those discussions may be different”* (Z6, site staff, site 2). Counselling was conducted *in the language of the participant’s choice* (Z10, site staff, site 5).

Across all sites, counselling was conducted by trained counsellors who were part of the site staff complement. While the baseline training of counsellors varied, it was reported that counsellors have undergone intensive network-driven training on risk-reduction counselling in efforts to systematise counselling across study protocols and trial sites. For example:

“...our counsellors undergo the training of risk-reduction counselling which was offered [by] the [network]” (Z2, site staff, site 1).

“... most recently...there was an effort to try and create standardised training material that was made available to sites so that all of the counsellors who are participating in the HIV prevention trials... could have a similar training experience so that at least from a [sponsor] perspective there would be a common platform you know when we say risk-reduction counselling, those counsellors have been through a common experience...” (Z6, site staff, site 2).

Some interviewees, including counsellors, commented positively that counselling was *in depth* and intensive. While risk-reduction counselling was primarily provided by a designated counsellor, at some sites it was reported that additional counselling on specific issues (e.g., access to PEP) was provided by other study staff (e.g., clinicians, nurses, etc.).

The master protocols for both trials specified that counselling should follow the US Center for Disease Control (CDC) guidelines for HCT unless alternative procedures are approved or mandated by the local REC. Interviewees described that risk-reduction counselling was developed in accordance with CDC guidelines but tailored to the South African context. Risk-reduction counselling was argued by one interviewee to be an *upgraded* (Z2, site staff, site 1) version of South African guidelines while another contended that South African guidelines were *excellent ... I found them much more comprehensive than what I could find the CDC* (Z13, network representative). Given that sexual activity is an enrolment criterion, at one site, the mantra of ABC was reported to be incompatible with trial requirements:

“They follow DoH counselling guidelines and CDC, but ABC in reality does not work! It is a song the counsellor needs to sing. Participants can’t abstain – we need the risk behaviour. They can’t say the ‘A’” (C1, site staff, site 1).

Interviewees described counselling sessions as a *“personalised”* risk-assessment where the counsellor could *“dig more details”* (Z4, site staff, site 2) about a participant’s risk behaviour and jointly develop risk-reduction plans. In addition, detailed behavioural risk-assessments (cf. Andrasik et al., 2013) were conducted by members of the research team. According to the phase IIB protocol, behavioural risk-assessments were completed at screening and in all but five study visits. The phase I protocol indicated that the behavioural risk-assessment questionnaire was only administered at screening. Phase IIB site documents revealed that an interviewer-administered risk-assessment tailored to males and females was administered to all participants. The risk-assessment comprised questions on sexual practices including number of sexual partners, HIV status of partners, sex of partner, condom use, type of sexual activity (vaginal, oral or anal), recent STIs, alcohol and drug use, transactional sex and forced sex.

From interviews, multiple objectives of risk-reduction counselling were identified. Interviewees at some sites described that counselling aimed to reduce unsafe sexual practices that may result from misperceptions of vaccine efficacy (i.e., behavioural disinhibition), for example:

“...they [participants] were told to stick to condoms... because the study is a research, it’s not approved” (Z1, CAB, site 1).

“...we try our level best to make sure that they [participants] understand it...every time when they come for follow ups that we should still try to ask them few questions to make sure that they do remember that while they are participating it’s not really protecting them. It’s a trial” (Z15, site staff, site 3).

The value of counselling for improving uptake of prevention interventions was also highlighted. Key aims of risk-reduction counselling included assisting participants in identifying their risk behaviours, helping participants reduce their risk (i.e., protect participants), and educating participants about potential risks.

When indicated, it was reported that participants were referred to psychologists or social workers for additional psychosocial support and counselling.

In both trials and at all sites, risk-reduction counselling was guided by a network-provided risk-reduction worksheet which was a comprehensive “*menu-based list of options that are explored with the participants*” (Z6, site staff, site 2). This worksheet comprised an assessment of the participant’s subjective perception of his/her HIV risk plus an objective exploration of potential risks for HIV/STI acquisition, including drug and alcohol use, sexual activity and type of sexual partners. It also involved developing plans for how the participant will reduce his/her risk behaviours and identifying any sources of support including referrals. The worksheet required that counsellors review with participants the changes that the participant had made post the last study visit, as well as any potential for risk compensation/behavioural disinhibition. Risk-reduction counselling is distinct from behavioural risk-assessments in that the focus is on identifying and minimising risk behaviours. Worksheets were also reported to serve as a guideline for counsellors:

“...we also have our worksheets which helps guide/ it sort of sets up the pieces that need to be covered during sessions and we’ve done training on the worksheets so that adds to it as well” (Z13, network representative).

The risk-reduction worksheet permitted chart-noting of counselling sessions, serving as a possible tool for documenting counselling sessions. In terms of monitoring practices, at some sites, respondents reported that the quality of risk-reduction counselling was assessed and that all risk-reduction documentation was quality controlled:

“...trials are monitored the way they are monitored? So, whatever they come, and they’ll look at your counselling forms. They’ll look at your chart-notes” (Z11, site staff, site 2).

“... we have a programme that staff members get assessed on a regular basis. So somebody would sit in a counselling session and actually write down you know, make notes of what’s said and what was left and you know what was missed and things like that and people then get retrained...” (Z17, site staff, site 5).

However, at some sites it was reported that supervision of counselling sessions, while ideal, was not possible due to staff shortages:

“...if we had enough counsellors, like... it will make more sense that you have somebody that sits in from time to time, but we are so constrained. Like in the/ in all the projects that I’ve worked in, I was the only professional counsellor” (Z11, site staff, site 2).

1.1.1 Complexities with risk-reduction counselling

1.1.1.1 Relying on self-report by participants

At some sites there was concern that risk-assessments relied on self-reports which are notoriously subject to social desirability bias (Chillag et al., 2006; van de Mortel, 2008), referring to the tendency of participants to respond in a way that presents a favourable image of themselves (King & Bruner, 2000). The participant may believe their self-report to be accurate (self-deception) or they may ‘fake good’ to conform to socially acceptable values, avoid criticism, or gain social approval (King & Bruner, 2000).

Since site staff build relationships with participants focused on reducing risk, participants in HVTs may have responded to questions about their risky behaviour in such a way as to please site staff or gain their approval, and may therefore not have reported their risky behaviours.

For example:

“So most cases we find people mention that they are using protection. At the end of the day, they not using protection because you find them with STIs, the others are pregnant, others are infected with HIV” (Z4, site staff, site 2).

“The common problems, you know, everybody used a condom, and everybody’s pregnant.” (Z11, site staff, site 2)

“...if the doctor wants an answer that’s yes, I’m going to say yes. That is the answer that the doctor wants.” (Z10, site staff, site 5).

Gendered stereotypes and cultural taboos were also noted to complicate self-reporting of risky behaviours, for example:

“... she just said she was scared to mention more than one partner. So that is why she keep on lying. She was so scared to mention more than one partner in her age and she’s a female. It was going to be better if she was a male.” (Z4, site staff, site 2).

Still, some interviewees argued that socially desirable reporting decreases as relationships between counsellors and participants develop. Because counselling was tailored to participants’ risk profiles, socially desirable reporting was described as an obstacle to effective risk-reduction counselling.

Self-report was also argued to be flawed because participants’ perception of their risk was inaccurate:

“...I think people themselves have a lot of trouble perceiving their own risk...” (Z18, site staff, site 5).

1.1.1.2 Participants’ implementation of risk-mitigation plans

In contrast, some interviewees reported that participants were forthcoming about their risk behaviours but the challenge was participants’ failure to implement risk-mitigation plans:

“...I’m usually of the view that people are telling us what they’re doing but I guess it is an issue whether or not they are then able to translate whatever insights they reach through the counselling process into some practical steps when they’re outside of the clinic” (Z6, site staff, site 2).

“...they are not practicing [safe sex] all of them because as a result they become pregnant, they seroconvert...because of their risk behaviour ‘uh, I was drunk, I went to the party, the condom burst and all that.’ They came up with the package of the excuses why they become infected” (Z2, site staff, site 1).

“...we offered an excellent standard of prevention. As I mentioned, sadly, we still had an extraordinary incidence rate. So, you know, it’s sobering that even when you offer all of those services, you still see a lot of HIV transmission.” (Z18, site staff, site 5).

A respondent at one site noted that a potential difficulty with changing behaviours, particularly for men, related to cultural conceptions of masculinity and cultural practices of multiple partners:

“... ‘cause men are the people, I don’t want to say stubborn, they still believe in their what? Is it inheritance? Where they’re coming from. They coming from polygamous families, so it’s very hard to change a person like that who’s born in a family where there’ve been five grannies, five mothers.” (Z1, CAB, site 1).

1.1.1.3 Supporting counsellors

The importance of providing continuous mentoring, training and psychosocial support for counsellors was mentioned:

“The first challenge with risk-reduction, or any counselling, is that you need to have a certain type of personality to provide the counselling itself, so that’s challenge number one. Training people, er, mentoring them, and supporting them throughout, because what we tended to realise is that you train people, and the first two weeks after the training, you go into the counselling session, you know, you are very impressed with the way the counselling goes on. Come month three, you go in, sometimes you don’t even believe it’s the same counsellor that you trained that is offering the counselling... Because everybody that comes in offloads onto the... counsellors, and by the end of the week the counsellors have absorbed so much that, you know, they don’t even look forward to go into the next week” (Z11, site staff, site 2).

“...our counsellors I think they have a very challenging job and it can be very hard on them emotionally and we’ve had to work on addressing that. And interestingly that

was in the area that was very much appreciated, that was one of their favourite topics with the training that we did.” (Z13, network representative).

One respondent also noted that despite the important role of counsellors in HIV prevention research, their salaries were not commensurate with their responsibilities in trials:

“...you get counsellors...they’re highly trained, they’re highly motivated, but if you look at counsellors throughout the country, if you look at their salary structure, and the important role that they are playing in your HIV prevention trials then you have to say, really... counsellors are very lowly paid, and that is a major concern...that is a demotivating factor” (Z10, site staff, site 5).

In support of counsellors, a mentorship programme was instituted at sites that elected to implement it. Counsellors’ mentors were responsible for training counsellors, debriefing them and providing general support, helping them deal with *“difficult clients or participants”* (Z2, site staff, site 1), and reviewing *“chart-notes”* of counselling sessions.

1.1.2 Comparing risk-reduction counselling practices with recommendations in ethics guidelines

All HVT sites satisfied ethics guideline requirements (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) that comprehensive risk-reduction counselling be provided to participants. MRC (2003) guidelines require that counselling be conducted in accordance with national guidelines. The South African guidelines for HCT (DoH, 2010) provide little direction on HIV prevention counselling. However, they do require that counselling be conducted in a language that the client understands, and that when HCT is conducted in the context of research, all participants *“must be informed about HIV prevention through practicing safe sex, and effective treatment or referral must be provided for STIs”* (DoH, 2010, p. 13). In addition, all clients who test HIV-negative should be offered a comprehensive prevention package that includes information about VMMC, TB screening, risk-reduction and the correct and regular use of condoms (DoH, 2010). Further, like ethics guidelines, national guidelines specify that counselling should be conducted by *“an appropriately trained, mentored, and supervised counsellor...”* (DoH, 2010). CDC guidelines recommended for use in both study protocols state that counselling should involve a risk-assessment based on the unique characteristics of the client as well as the development of concrete risk-reduction goals (CDC, 2001). It is also recommended that counselling be provided on-site by trained counsellors and that counselling should be monitored for quality

(CDC, 2001). In practice, trial participants in both trials received risk-reduction counselling in accordance with CDC guidelines and South African national guidelines.

The provision of psychosocial support for counsellors was also identified as critical in previous research (Heise et al., 2008). Given their ongoing relationship with trial participants over the course of the trial, counsellors may experience high job stress and burnout and there is a need for increased support of counsellors through opportunities to debrief and counselling (Heise et al., 2008).

Key reported concerns with social desirability are anticipated by select guidelines which outline that site staff should be cognisant of the potential for social desirability bias and recommend the use of neutral advisors and trained counsellors (MRC, 2003). Previous research has recommended that ongoing assurance of confidentiality to participants may circumvent some concerns that full disclosure may result in stigma, ridicule and gossip (Chillag et al., 2006). Given cultural barriers to discussing sex with older persons and persons of a different gender, it was recommended that where possible, same-gender and similarly aged research staff should be selected (Chillag et al., 2006). Reported complexities also reflect broader concerns with the efficacy of counselling to reduce HIV risk and underscore the search for an expanded array of prevention options that combine biomedical and structural interventions with behavioural interventions (Hankins & de Zaluondo, 2010).

1.2 Ensuring access to male and female condoms

If used correctly and consistently, condoms are an effective strategy for preventing HIV. Ethics guidelines specify that trial participants should receive access to male and female condoms (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), with appropriate instructions and demonstrations (UNAIDS/AVAC, 2011).

In practice, at all five sites, and for both trials, male and female condoms were reportedly provided to participants during risk-reduction counselling sessions and participants were counselled to use condoms with every sex act. According to interviewees across sites, condoms were available outside counselling sessions, for example, at reception, in restrooms and waiting areas. The availability of male condoms at sites was also observed by the researcher during visits to trial sites.

At all sites, participants received condom demonstrations using a penile model. At one site it was reported that while vaginal models were also used, female condom use was only partially demonstrated (Z2, site staff, site 1).

At all sites, condoms were procured from the DoH at no cost to sites. At one site it was reported that condoms were also sourced from a donor. The risk-reduction worksheet used by all sites required chart-noting (recording) of condom provision, which was also reported to facilitate feedback to the DoH on the number of condoms issued.

1.2.1 Complexities with condoms

1.2.1.1 Ensuring adequate supplies from government partners

At two sites, shortages of government-issued male condoms were reported:

“Sometimes you find that the condoms are not available from the provincial office...”
(Z8, site staff, site 4).

“Well there are times when it’s not available...it would relate to the general shortage of condoms” (Z10, site staff, site 5).

However, at these sites, staff did not explicitly report that shortages in supply resulted in instances where no condoms could be provided to participants.

There were reports about particularly poor accessibility of female condoms at all sites, for example:

“...the majority are really male condoms because you know to access female condoms is a mission and they are expensive” (Z22, site staff, site 1)

“...we didn’t have as many female condoms. I think we had a problem getting the condoms, and we had demands” (Z11, site staff, site 2).

Given the limited availability, at some sites it was reported that female condom provision was capped or only provided on request because they *“...are provided very sparingly from the Department of Health with the proviso that only females who request it are actually dispensed those condoms...”* (C7, site staff, site 4).

1.2.1.2 Counsellor promotion of condoms

Interviewees at some sites reported that condom use was emphasised:

“We actually encourage them to use condoms... we emphasise that they must use condoms” (Z8, site staff, site 4).

The emphasis on condom promotion was partially driven by the requirement to record or “chart-note” condom provision on the risk-reduction worksheet:

“When you counsel someone you have to issue condom, and you have to ...chart-note that I issue so much condom to the participant” (Z2, site staff, site 1).

Since risk-reduction worksheets were reviewed by mentors, it was reported that participants may be pressured by counsellors to take condoms, for example, participants “cannot get out of the [counselling] room without a condom” (C1, site staff, site 1). Condom provision was described as a tick-boxing activity by one respondent - “it became a quantitative issue, not a qualitative thing” (C1, site staff, site 1).

1.2.1.3 Low acceptability and uptake by participants

At two sites it was reported that participants had complained that “the Department of Health is not providing worthy condoms” (Z3, CAB, site 2). Complaints included that these Choice condoms break, are too small and may cause allergic reactions. Trial participants were reportedly unhappy that they were provided with “the same condoms as in the public service [sector]” and they “expect that the researchers need to give them the best” (C1, site staff, site 1). To remedy concerns, one site secured condoms from an international donor while at the other site some participants reportedly opted to purchase their own condoms:

“Yes, so they don’t want it at all...they prefer to go and buy the condom from the pharmacy” (Z4, site staff, site 2).

“I’m providing condoms, since we are using the government condoms, the Choice condoms, so if a particular person says, you know what, I don’t want condoms, I do go to the garage and buy them, you write down in a chart-note that I’ve offered condoms to this particular participant but he said he’s ok, he’s using the expensive condoms...” (J1, site staff, site 2).

It was noted that participant acceptability of condoms may be related to the cultural perceptions of the inadequacy of Western medicines which may inhibit condom uptake, especially by male participants:

“...you get the very very traditional guys they don’t believe in Western medicines, they don’t believe in condoms...” (Z8, site staff, site 4).

There were reports of poor uptake of female condoms at most sites. Respondents across sites described various reasons for poor uptake including that it is “*not comfortable*” (Z7, site staff, site 1), “*it makes a lot of noise*” (Z15, site staff, site 3) and “*is too big for them*” (Z4, site staff, site 2). Further, female condoms “*are not user friendly, you’ve got to put them on quite earlier on, and so those messages are not attractive*” (Z22, site staff, site 1).

1.2.2 Comparing condom practices with recommendations in ethics guidelines

Consistent with ethics guidelines, access to male and female condoms was ensured for trial participants (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Obligations to ensure access to condoms entail that they should be available at or in close proximity to the trial site, and there should be no economic or other barriers to their attainment (Lie et al., 2006). Therefore, it could be argued that at most sites, obligations to ensure access to female condoms were not wholly satisfied (see Chapter 11 for detailed discussion). While guidelines are silent on issues of poor uptake, national guidance requires that risk-reduction interventions be monitored for quality, specifically the “availability of adequate supplies of barrier methods” (MRC, 2003, p. 31).

Collaborating with host country governments in ensuring the highest standard of prevention is a requirement of ethics guidelines (UNAIDS/WHO, 2012). Trial sites have indeed partnered with government stakeholders (namely, DoH) to ensure access to free condoms for participants. The reported challenges with procuring condoms from government partners suggest that constant engagement with such stakeholders is critical. Further, sites should plan for inadequate supply by government partners, given reports that in 2010/11 the DoH fell short of their targets for the distribution of both male and female condoms (DoH, 2011). While one strategy may be to seek supplies from international donors, it must be ensured that these condoms comply with South African Bureau of Standards (SABS) requirements.

The concerns by some participants that *Choice* condoms are of inferior quality may relate to the recall of these condoms by the South African government (Moszynski, 2007), three times in less than five years. In August 2007, 20 million condoms were recalled after it was learned that a testing manager at the SABS had accepted money from the manufacturer in exchange for certifying defective condoms (Reuters, 2007, in Moszynski, 2007). In October 2007, an additional five million condoms were recalled after a sample failed the airburst test (BBC, 2007, in Moszynski, 2007). Further, Lindegger, Solomons, Essack and Blackbeard (2007)

found that young men were reluctant to use freely available government condoms because they believed that these condoms did not help them sustain a particular image or status. In keeping with reports in this study of participants opting to purchase their own “expensive” condoms, “the use of a brand label helped create and maintain status and reputation for young men in relation to partners and social reference groups” (Lindegger et al., 2007, p. 26). More recently, the DoH acknowledged “condom fatigue” among target users as well as the perception that *Choice* condoms are “uncool” (BBC News, 2 April 2014). In response, the DoH planned to introduce colourful and flavoured condoms (BBC News, 2 April 2014).

1.3 Ensuring access to STI treatment

STIs are proven cofactors that significantly increase vulnerability to HIV (WHO, 2003). Ethics guidelines require that access to STI treatment should be ensured for trial participants (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) and that risk-reduction counselling should include education on general health and the treatment of STIs (UNAIDS/WHO, 2012).

At all sites and for both trials, participants were counselled on how to prevent STIs. In concordance with the phase IIB protocol, it was reported that sites followed South African national guidelines for STI treatment, i.e., syndromic management (DoH, 2008). Syndromic management entails identifying symptoms and providing treatment for all infections that could cause those particular symptoms, for example:

“...if they have a symptomatic episode they’ll be examined and their history taken by one of the study clinicians and an assessment made.... A clinician will make an assessment by what kind of syndrome they have and apply the (unclear) syndromic management” (Z6, site staff, site 2).

“For each visit our participants require physical examination...it is a symptom-directed physical exam... if a participant complains specifically of a discharge, warts or whatever it may be, even if they’re unsure, then I would do genital exam, a genital-urinary exam to exclude an STI or if the participant complains of a discharge then I would examine the participant, confirm that they do have a discharge which requires STI treatment and then I would treat them for it” (Z7, site staff, site 1).

At four sites participants received STI treatment on-site, for example “the site provides STI treatment” (C9, site staff, site 4) and “we provide STI treatment on-site” (Z17, site staff, site 5). At one site, participants were referred to public healthcare facilities: “STIs we don’t provide that on-site... We sending them to a local clinic to get that” (Z15, site staff, site 3).

If an STI remained unresolved post-treatment, participants were referred to the public healthcare sector for further care, for example:

“...if there’s a sort of treatment failure in that regard, then they would be referred to the local clinic” (Z10, site staff, site 5).

“...for those that we could not treat we were still referring it’s either to the/ depending on the severity, it was to the hospital or to the clinics where they would treat” (C8, site staff, site 4).

Respondents described that donor restrictions prohibited the use of research funding for care services (detailed in the section on complexities below). Various strategies were therefore adopted at sites to enable on-site treatment, including procuring STI drugs from the DoH, and site-funded treatment. It was reported that where the site was unable to devise its own strategy, the network was able to support certain sites to provide on-site treatment:

“...but because of the cost of these being quite minimal we’re able to procure resources if the sites themselves are not able to do so. Usually the sites themselves are able to procure sufficient resources for something like that” (C14, network representative).

For the phase I trial conducted at two sites, it was reported that STIs were addressed by on-site treatment, with the drugs being funded by the affected sites, for example: “... we purchase it ourselves as an organisation” (Z17, site staff, site 5).

1.3.1 Complexities with STI treatment

1.3.1.1 Sponsor restrictions of funding

A key reported challenge was that trial funds come with restrictions ó certain sponsors do not permit the use of funds for non-research activities, including the procurement of drugs:

“But [sponsor] money is restricted in that it has to be used for research. It cannot be used for care and that is a very clear distinction. That’s a distinction that takes a [government] to change... So for example unless an STI test is mandated by the research we cannot cover the cost of that test” (C10, network representative).

“The research costs are of course all-encompassing within these protocol costs but other costs such as you know treatment of medical issues not directly related to the protocol defined objectives can be problematic and this includes treatment of STIs for example. Unless we’re doing a prevention study that’s focusing on comparing the treatment of certain STIs versus others so payment for drugs that is not study product is usually not allowed...” (C14, network representative).

Concerns about funding restrictions were also raised by respondents at sites, for example:

“...there is a clause from the [sponsor] that they cannot spend their money on drugs...at some level it feels a bit like a cop-out...it just seems to be one of those things that you just can’t raise and discuss, you know, so it gets stuck...” (C11, site staff, site 5).

1.3.1.2 Using the syndromic management approach

Interviewees at some sites reported complexities with syndromic management, for example: *“STIs are really over and under treated in our population” (Z7, site staff, site 1)* and *if they don’t report symptoms, we don’t know.” (Z6, site staff, site 2).* It was argued that there is a need to develop better methods to diagnose STIs.

Cultural barriers with discussing sexual activity and related issues, especially with someone of the opposite sex, may also impede self-reporting of STI symptoms, for example:

“...one of the participants, I mean he’s been coming here for three years and then he tells me the other day that you know he’s been having a urethral discharge. So I say you know when did it start? So he says no about four or five months ago. I’m like gosh and I saw you in between that time and you didn’t tell me about it. So he says no. I think he was just embarrassed because he’s male and maybe I’m female. I think it’s a barrier sometimes with [name of ethnic group] men” (C2, site staff, site 1).

However, others contended that syndromic management is a better approach in trials:

“I think it’s working well because laboratory support is not always what it should be. It’s much better in research... It enables you to start treatment for a participant prior to getting a laboratory result” (C7, site staff, site 4).

“I mean for [the phase IIB] we did go back and forth quite a bit on to what extent do we screen and diagnose and treat STIs and prescribe that in the protocol... if going to really diagnose it then you need to collect sufficient samples and you need to culture it in a variety of ways, you need to have the diagnostic infrastructure sufficiently on the ground” (C14, network representative).

1.3.2 Comparing STI treatment practices with recommendations in ethics guidelines

All sites satisfied guideline requirements by counselling participants on how to prevent and treat STIs (UNAIDS/WHO, 2012) and ensuring access to STI treatment (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

STI treatment can be ensured in through syndromic management based on self-report of symptoms or by testing for all STIs (intensive diagnostics). MRC (2003) and UNAIDS/WHO (2012) do not prescribe whether diagnostic tests or the syndromic management approach should be adopted. While UNAIDS/AVAC (2011) specifies that STI testing should be

discussed, and its appropriateness for the trial design and population assessed, the provision of syndromic management is in line with WHO (2003) recommendations and South African STI treatment guidelines (DoH, 2008).

The over-diagnosis and over-treatment of STIs as a result of syndromic management are acknowledged as a potential disadvantage in the literature (Altini & Coetzee, 2005) which has implications for increased drug costs and potential drug resistance, among others. Further, it has been argued that South African guidelines of syndromic management may be inadequate or not in participants' best interests (cf. Essack, Koen & Slack, 2009). However, the syndromic approach permits healthcare providers to make a timely diagnosis without specialised skills, and sophisticated and costly laboratory tests (Altini & Coetzee, 2005). In South Africa, syndromic management of STIs is free, integrated into primary health centres, and available in public health clinics (DoH, 2008; Heise et al., 2008).

1.4 Ensuring access to VMMC

Three RCTs of VMMC found that male risk of contracting HIV during heterosexual intercourse is halved when circumcised (Weiss et al., 2008). In 2007, WHO and UNAIDS issued recommendations on VMMC as an additional HIV prevention strategy based on strong and consistent scientific evidence. International ethics guidelines also require that access to VMMC be ensured for participants, where indicated (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

At all affected sites, interviewees reported that participants in the phase IIB trial were informed of the benefits of VMMC and that it was provided to all male participants who requested it. At the time the trial was initiated, VMMC was not widely rolled-out in the public sector:

“You know it’s not regularly available. If you referred someone to [public hospital] they’re going to wait for over a year to have a circumcision done.” (Z7, site staff, site 1).

Given the poor availability of VMMC at the time (de Bruyn et al., 2007) and the prohibition on the use of donor funding for care services, circumcisions were paid for via funds sourced from the product developer for the phase IIB trial:

“We have a sponsor [the product developer] that’s paying for male circumcision...” (Z17, site staff, site 5)

“...the largest trial that we conducted... [the product developer] actually provided the funding for the circumcision procedures” (Z9, network representative).

For the phase I trial, VMMC was not paid for by the sponsor nor were alternative funds secured. However, it was reported in interviews at both sites conducting the phase I trial, that VMMC was made available if requested.

At four of five sites, VMMC was ensured through referral to the private sector, for example:

“You know they [the network] provided the money so our participants could get circumcision in private but because it was (not) being rolled out uh (R: nationally) in the public sector, ja, at that time.” (Z7, site staff, site 1)

“...the circumcision we made an arrangement with a local GP, we were not sending them to the public sector, we were having that special arrangement with the GP who has to do that for our participants.” (Z15, site staff, site 3)

“Well the one classic one that we do quite a bit of is our circumcision. So our circumcisions are done by a private practitioner, a private surgeon, and that’s just because then it’s just easy. It’s just been easier and cleaner.” (C11, site staff, site 5).

At one site, VMMC was provided on-site by a trained individual:

“...for our site you know it’s easiest to implement in a situation where uhm you know a trained individual uhm came and performed the procedures for trial participants who wanted to be circumcised” (Z6, site staff, site 2).

It was argued that referral to the private sector was a strategic decision in order to avoid the challenges of the public healthcare system:

“...we initially thought of going through the public system...but it’s a mission...people are put on theatre lists and you know how it gets when somebody doesn’t pitch and they don’t get operated that day it’s a mission. So we went the private route which is much easier” (Z17, site staff, site 5).

“...we were aware of what the limitations were of the local health services and uh that just telling people about it wouldn’t/might mean that they’d have to wait years, if ever, to get a procedure” (Z6, site staff, site 2).

1.4.1 Complexities with VMMC

1.4.1.1 Ensuring access to VMMC across trials (funding for VMMC)

Interviewees at one site asserted that paying for VMMC in one trial, and not in others, created differences between participants at different sites or in different protocols, for example:

“[The phase IIB trial] also funded circumcision for males and none of our other planned or current vaccine trials actually support that. So we do refer people to the public sector with counselling but we don’t have any influence over how soon that care is accessed...” (C7, site staff, site 4).

However, such concerns may decrease over time as referral for VMMC becomes increasingly acceptable, given scale-up in the public healthcare system ó from one VMMC site in 2010 to over 80 sites by 2012 (Rech et al., 2014) ó so sites ö...would probably in the future deal with participants wanting circumcision by referring themö (Z6, site staff, site 2).

1.4.1.2 Provider-promotion of VMMC

Respondents at some sites expressed concern that low uptake may reflect poor provider-promotion of circumcision, for example: öí there was even a joke of saying that maybe it’s because the investigator sometimes may not really be for circumcision...ö (Z15, site staff, site 3). It was asserted that sound counselling was key to improving uptake of prevention interventions: öí if the participants are counselled adequately then the uptake will be goodö (Z7, site staff, site 1) and öIf they’re just given everything, and they’re not counselled about what the implications are of taking it or not taking it, then you’ve got a problemö (Z12, REC member).

1.4.1.3 Participant acceptability and uptake of VMMC

At certain sites, the uptake of VMMC was reportedly good. Some even reported the provision of circumcision as a success: öI think it’s the one thing I can say it’s a highlightö (Z2, site staff, site 1) and öin terms of things that have worked well, I mean I think definitely in our hands offering male circumcision has been taken up quite widelyö (Z6, site staff, site 2).

However, at two sites, interviewees reported lower uptake, attributed to preferences for traditional circumcisions in the wider community: ö...you have to realise that we live in a community where male circumcision is part of a customö (Z10, site staff, site 5). Therefore, many participants may already be circumcised or may prefer traditional circumcision: ömany people feel they don’t want to come do it on-site, so they will wait for the right opportunity and go and do the traditional way out in the veldö (Z15, site staff, site 3).

Despite initial concerns about low acceptability and stigma due to cultural taboos around circumcision, interviewees reported a high uptake of VMMC in those areas with the lowest baseline circumcision prevalence:

“...when we told [the investigator] ...that we were doing circumcision, I remember her eyebrows shot up, um, and she was sort of surprised, and thinking, ‘Oh. Well that’s never, you know, that’s never/ we’re never going to be able to get much uptake of that...ironically, and I think happily for her, she was wrong, there was a good uptake” (Z13, network representative).

“...we were actually very surprised [by the high uptake of VMMC] because you know, all the stigma that’s attached to being circumcised here” (Z7, site staff, site 1).

While concerns about the cultural acceptability of circumcision are widely published (Eaton & Kalichman, 2009; Khumalo-Sakutukwa et al., 2013; Mark et al., 2012), a few respondents in this study expressed some concern that circumcision served as an inducement to participate, even in contexts where circumcisions are not traditionally practiced.

1.4.2 Comparing VMMC practices with recommendations in ethics guidelines

In concordance with international guidelines (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), VMMC was provided to all willing participants, where indicated. South African guidance (MRC, 2003) was drafted before the VMMC results became available. Therefore, they do not specify that VMMC be provided but they do require that new tools should be added to the prevention package as they are discovered and validated.

Low uptake reported at some sites (attributed to cultural objections) resonates with complexities theorised to be of some importance by ethics commentators (cf. Lie et al., 2006; HPTN, 2009) including that VMMC presents òfundamental cultural issues for implementationö (Haire et al., 2012, p. 23). Low uptake at sites located in traditionally circumcising communities was also consistent with research findings (Mark et al., 2012) and acceptability is likely to be context-specific and influenced by local cultural norms and practices (Eaton & Kalichman, 2009). Mark et al. (2012, p. 571) found that while the majority of men in the sample were aware of the preventive benefit of VMMC, most were òunwilling to undergo a medical circumcision or allow their sons to do so, because of religion/culture, notions of manhood, and social disapproval.ö Other research in traditionally circumcising communities in Tanzania found that despite a preference for VMMC, traditional circumcisions are still practiced due to social pressures in the community (Wambura et al.,

2011). However, the uptake of VMMC reported by interviewees in this study, albeit low in traditionally circumcising communities, suggests that for some individuals offers of VMMC may still be accepted. Therefore, access systems for such services should be considered regardless of the cultural context. Offers of VMMC should not be censored based on predominant social, cultural or religious values in a community (Haire, 2013).

1.5 Access to PEP

Emergency PEP with antiretroviral drugs is the standard of care for occupational exposures to HIV through infected tissues or fluids, and is increasingly used for nonoccupational exposures (Tolle & Schwarzwald, 2010). Across all trial sites, and for both trials, interviewees reported that PEP was provided to participants on-site for all risky sexual exposures. During counselling sessions, participants were reportedly informed that they need to report to the site “*within 72 hours*” (Z7, site staff, site 1). Some sites reported implementing strategies to facilitate prompt reporting.

For the phase IIB trial, it was reported that at most sites PEP packs were available on-site (procured from the DoH or other sources like PEPFAR), for example:

“...I was privileged that within [name of trial site] we also had a treatment/ an HIV treatment programme which then made eh provision of eh post-exposure prophylaxis easy because we had antiretroviral drugs on-site” (Z22, site staff, site 1).

In some instances, arrangements were brokered with other sites to facilitate access to PEP. For the phase I trial, interviewees at both sites reported that the site covered the cost of PEP provision.

One respondent noted the potential for participants to misuse PEP: “*it’s like uh TOP [termination of pregnancy], you know, some people don’t use contraception, they just go have TOPs all the time, it’s the same thing, you know*” (Z7, site staff, site 2). However, another respondent noted that PEP is unlikely to be abused due to severe side effects:

“...even within our SOP, we would not hand out post-exposure prophylaxis repeatedly... and then you know, they could do this again, and possibly even again (laughs) but there’s a point at which the staff would really step up with their risk-reduction counselling, and to be honest...it’s not my experience that people abused this service, or kept using this service...” (Z18, site staff, site 5).

In line with the latter view it was reported that the uptake of PEP was low: *it's not the most popular thing* (Z18, site staff, site 5) and *I can't remember the numbers exactly, but I think it was pretty small* (Z9, network representative).

1.5.1 Complexities with PEP

1.5.1.1 Initiating PEP using non-government guidelines

The national protocol for the provision of PEP in the public sector is limited to sexual assaults and not for other risky sexual exposures, like condom failures. However, for the two trials sampled in this study, PEP was provided on-site for all sexual exposures:

"...in South Africa it's usually given in the public sector for post-rape, post-needle stick injuries, or whatever, but because we're funded by [the network] and...they follow the US sort of guidelines with regard to HIV prevention" (Z7, site staff, site 1).

"...in fact offering PEP is over and above what somebody would get in the public sector at the moment" (Z18, site staff, site 5).

Given the South African PEP protocol (DoH, 2008), some interviewees questioned the provision of PEP for all sexual exposures:

"...things like post-exposure prophylaxis, we don't in fact provide to everyone who's having unprotected sexual intercourse, and we provide it in very limited situations, mainly the context of sexual assault. So it's not clear to me in South Africa whether or not post-exposure prophylaxis is in fact an appropriate thing to provide in a vaccine trial" (Z16, REC member).

An interviewee at one site stated that offering PEP in the phase IIB trial created an incongruity amongst participants enrolled in different protocols:

"I think the one challenge I've experienced and this had been a difference between [the phase IIB] trial and our other vaccine trials is that in [the phase IIB trial] we provided post-exposure prophylaxis for risky sexual contact, it didn't have to be a sexual assault. But for all our other protocols we follow the national department of health guidelines because PEP is not provided by the protocol budget...as a consequence we can only refer people for post-exposure prophylaxis if there's been an actual sexual assault..." (C7, site staff, site 4).

1.5.1.2 Provider-promotion of PEP

Some interviewees expressed concern about the lack of evidence from RCTs to support the efficacy of PEP as well as safety concerns. One interviewee stated: *"...we don't have direct evidence that it works"* (Z6, site staff, site 2). Another remarked that PEP provision is *not*

necessarily in the patient's greatest safety interests" (Z16, REC member). However, others suggested there was sufficient evidence to support the use of PEP, for example:

"...my own belief around this is that there is sufficient evidence to believe that it is effective" (Z18, site staff, site 5).

"... we are living in such a high prevalence you know eh environment of HIV and so really I would still encourage to an extent post-exposure prophylaxis." (Z22, site staff, site 1).

An interviewee at one site reported that PEP was provided inconsistently because of provider-beliefs about efficacy: *"some people provide it, some people don't"* (Z6, site staff, site 2) and described PEP as *"a very un-standard part of the study"* (Z6, site staff, site 2). At two sites, it was reported that the use of SOPs may help improve standardisation.

Even the level of counselling on PEP at two sites was reportedly not as intensive as for other preventive interventions, for example:

"So participants were counselled on the availability of PEP and then when we saw that... we were getting more and more seroconversions, then we counselled them for a second time to let them know that PEP is available here" (Z7, site staff, site 1).

R: *And do you discuss uh post exposure prophylaxis in your risk-reduction counselling?*

Z4: *No::t that much. Not that much. (Z4, site staff, site 2).*

1.5.1.3 Facilitating timely access to PEP

The requirement that PEP be provided within 72 hours of exposure was reported as challenging:

"...after 72 hours, we feel that the benefit, is not, um, sufficient for the side-effects and the risks, so we don't offer it after 72 hours. So it does mean the individual has to recognise their risk, and get into the clinic within 72 hours, and that is, tricky for a lot of people" (Z18, site staff, site 5).

A few respondents noted that some participants reported sexual exposure when it was too late to intervene, some only at seroconversion. In anticipation of problems with late reporting, some sites employed strategies to facilitate prompt reporting, for example:

"...sometimes we'd have participants who during holidays and over the weekend have contacted our site, uh but we did make the provision that we have a 24 hour cell phone available, so if a participant wants to contact us over the weekend and then we had a pack available" (Z7, site staff, site 1).

“Yes because they even call if maybe the condom was break. They even call over the phone then we’ll tell them come to the clinic” (Z4, site staff, site 2).

1.5.2 Comparing PEP practices with recommendations in ethics guidelines

South African guidelines (MRC, 2003) require that participants be informed about the benefits of PEP and where it can be accessed, while international guidance requires that participants are actually ensured access to PEP, where indicated (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). All sites satisfied international ethics guideline requirements by providing on-site access to PEP in the event of a known likely sexual exposure, and not only for sexual assault. This exceeded South African guideline recommendations (MRC, 2003) and the national protocol for PEP access in the public sector (DoH, 2008).

The provision of PEP at sites appears to be in line with the ethical vision of UNAIDS/WHO (2012) guidelines to prevent double standards between well-resourced and resource-constrained contexts (Haire et al., 2013). However, at an earlier regional consultation on ethical issues in preventive HVTs (UNAIDS, 2000, p. 20) it was argued that PEP “should be offered to trial participants to the degree that it has become the standard practice in the host country.”

There are some concerns with providing participants with access to PEP for all sexual exposures when this is not routinely available in the public healthcare sector. Firstly, some contend that providing PEP to participants when it is unavailable to the general population may be an inappropriate inducement to participate in the trial (UNAIDS, 2000). Secondly, it may increase disparities between trial participants and the local community (HPTN, 2009). However, UNAIDS/WHO (2012) justifies access to prevention services not locally available on the basis that participants bear greater risk than other community members by exposure to an experimental intervention (Haire et al., 2013). Still, as indicated by the data in this study, efforts to reduce disparities in the standard of prevention between well-resourced and resource-constrained contexts, may inevitably create differences between trial participants (see Chapter 11), both within and across sites. Thirdly, it is not sustainable post-trial. However, the immediate potential benefit of reduced HIV infection risk for trial participants is a legitimate benefit for the community, even when such services are not sustainable post-trial (cf. Haire et al., 2013). This perspective is espoused given that researchers should endeavour to “ratchet up” care in the local community (Shapiro & Benatar, 2005), where

feasible, and where the provision of such prevention services does not negatively affect the scientific validity of the trial.

1.6 Ensuring access to HIV prevention interventions for non-enrolled persons

Ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) are generally silent on the specific prevention services owed to persons not enrolled in trials, except for the provision of couples counselling (UNAIDS/AVAC, 2011) and informing participants about how to obtain STI treatment for their partners (MRC, 2003). In addition, UNAIDS/AVAC (2011) recommends consultation on the specific HIV prevention interventions that will be available to participants and partners. There are also general statements that those volunteers who screen out of the trial should be referred, where relevant (MRC, 2003) and provided with information about HIV prevention interventions available in the community (UNAIDS/WHO, 2012).

All sites reported providing some prevention services to persons not enrolled in trials, namely, volunteers at screening, participants and partners and the wider community. HIV prevention education was a commonly reported practice across all trial sites, for example:

“... we’ve got an obligation, of making sure that when we leave the community...they are better off...and one of the resources that we have, it’s knowledge. So we share information with the communities and the participants...” (Z11, site staff, site 2).

CAB interviewees also described their various HIV prevention education activities in the broader community, for example:

“With HIV prevention, I’m talking to people. As a teacher, I’m talking to the parents when we have parents meeting, talking to the children about HIV, how people can prevent HIV” (Z1, CAB, site 1).

“... there was intensive education given to people ... And when we say ongoing counselling on risk-reduction...it’s extensive shall I say education or enlightenment. Because now education would sound like one stream but we do dialogue with the communities and also guiding them to you know, the best practice that they could do, to prevent HIV and AIDS.” (Z3, CAB, site 2).

Both study protocols stated that risk-reduction counselling was to be provided to all volunteers at screening. In addition, some sites reported providing counselling to participants and partners via couples counselling, and to community members at the level of VCT as part of site activities.

Condoms were reportedly made available to partners in that participants were free to access male and female condoms. Condoms were also dispensed at community events and community members could access condoms at sites, for example:

“...on a monthly basis we have an activity that involves the community advisory group... where we do condom distributions.” (Z8, site staff, site 4).

According to both study protocols, volunteers underwent a physical exam at screening. Volunteers presenting for the phase I trial were screened for syphilis and if infected, were not enrolled. For the phase IIB trial, some sites reported that volunteers with STIs at screening were enrolled after successful treatment. Various mechanisms for ensuring access to STI treatment for volunteers were adopted across sites and for both trials, including, on-site provision (where funds permitted), or referral to a co-located or public healthcare facility, for example:

“Well we do offer STI and contraception services to anybody who accesses screening so it’s not quite the broader community but it’s broader than just the study sample that we’re looking at...” (C7, site staff, site 4).

“If they have an STI we would treat, because we have very much a policy of you, you know, don’t squander your opportunity” (C11, site staff, site 5).

“So what we would either do is, if the participant is comfortable buying the medication themselves, we would do the prescription here, but if, they cannot afford that, we would refer to the clinic, for STIs, it would be the clinic (C3, site staff, site 2).

Some interviewees reported that participants were informed about where their partners could access STI treatment. However, most respondents across all sites reported that partners were referred to the public sector, with a yellow card or referral letter/slip, for example: “...we give an STI referral slip for partners...” (C7, site staff, site 4). A few interviewees at some sites reported that, where possible, partners were provided with STI treatment on-site while others described lack of resources as an obstacle to on-site provision:

“We, unfortunately, do not have in place yet the STI treatment for partners which is, we’re planning to do that next year it’s just a bit of a resource issue because none of the sponsors will that pay that extra for partners because you know some people might five or six partners” (Z17, site staff, site 5).

For the phase IIB study, a circumcision assessment was conducted at screening and it was reported that volunteers were informed of the benefits of VMMC during risk-reduction counselling:

“...we informed everybody about the benefits of circumcision, we did do that. So even if they screened out and/ they were informed about circumcision so they could have gone to their local hospital but we didn’t actively refer them if they were screened out” (Z7, site staff, site 2).

“Ja as soon as they enter the pre-screen protocol. That includes information about circumcision, how to prevent HIV in general, you know condoms and teach for behaviour, they get pre- and post-HIV test counselling, they get risk-reduction counselling” (Z17, site staff, site 5).

At one site, it was reported that where female participants requested circumcision for their partners, they were referred to a local clinic. Access to PEP was ensured for enrolled participants only, at all sites.

Some REC respondents commented on researchers’ obligations to non-enrolled persons. The general sense was that there were limited obligations to these moral groups, including education on HIV prevention and referral to appropriate services:

“...for me there’s not ancillary care obligations to the wider community, except to maybe do engagement sessions and invite anybody who wants to come to them. And in those engagement sessions, speak about risk-reduction etcetera.” (Z12, REC).

“I think there is a moral hazard here that one will attract people...once you know a site is offering a very good screening service, you know, you may well be/ you could have a condition and go there purely to get screened...So, here you’ve got a kind of, an on-site service (.) so I think there’s that danger...obviously if it’s a heart transplant, you know, you would refer (laughs). If it’s a simple, you know, treating an STI, again I think we’re into/ I think, your obligations are less at this stage, but there are obligations to refer, to either your own ST/ and if you are already running your own onsite service to treat the common primary healthcare things and maybe (.) again have a strict referral thing.” (C6, REC).

“... there are things which are maybe perhaps should be obligatory and there are things which would be nice but not mandatory. And I think the principal obligation is in fact to the participant. I don’t know that it’s appropriate to make a broader community based contribution required of any trial but I do/ it would be nice and it would be part of the indirect benefit of the study’s existence...” (Z16, REC).

1.6.1 Complexities with ensuring prevention interventions for non-enrolled persons

1.6.1.1 Limited funding and resource allocations

As previously described, there were restrictions on the use of donor funding for non-research activities or care elements, including the provision of certain prevention services not considered necessary for the conduct of research. Further, some interviewees stated that the

provision of prevention services to non-enrolled persons was dependent on the trial budget, and that in a context of constrained budgets, it was difficult to ensure access to such services, for example:

“...you can have theoretically, you’re saying that standard of care must be provided to the whole study community... in real life it doesn’t actually doesn’t work like that. You know, you, you go and tell PEPFAR that, they’ll laugh in your face, they’ll say ‘Sorry, we’re not going to fund it.’ Or NIH is going to say, ‘We definitely don’t fund this.’” (Z12, REC).

“...I think it depends on the funding. You know, if the funding they would say, “Just service everybody”, then it would be nice. So, now we just have to depend on the other services, especially the government services, to refer them [non-trial participants] to.” (J1, site staff, site 2).

“We would like to add the STI treatment and you know just in general so anybody can come and get treated because then you know at least they do get treated but ja it’s a resource issue. It’s also very labour intensive.” (Z17, site staff, site 5).

1.6.1.2 Difficult to define partners

The presence of multiple partners was noted by some respondents as a key risk factor among the trial population. Some interviewees said that it was difficult to define obligations to partners because conceptions of partners may differ practically and culturally from theoretical definitions, and may infringe on participants’ rights or the rights of their partners:

“And in partners in particular I think there’re concerns because how participants define and choose to identify their partners to study staff is up to them, and in fact there’s the potential...for a study that wishes to engage with partners to be intrusive and to violate the rights of an individual participant.” (Z16, REC)

“...what if they have five sexual partners? What do you do if they have five sexual partners and a wife, or, you know a statutory wife, a common law wife, a customary wife, and a girlfriend? Where do you draw the line?” (Z12, REC)

“.... we try to offer services to partners. People have got multiple partners...not everybody has got a stable relationship...And, the communication that happens within those relationships, it can never be the same, and can never be standardised...as much as we are open to offering to partners, how we define partners as researchers or academics is completely different from what is happening on the practical basis.” (Z11, site staff, site 2).

1.6.2 Comparing HIV prevention practices for non-enrolled persons with recommendations in ethics guidelines

Site practices for non-enrolled persons generally exceeded requirements in ethics guidelines by providing access to selected HIV prevention interventions.

Consistent with GPP guidelines (UNAIDS/AVAC, 2011), some sites reported providing couples counselling. Sites exceeded guideline recommendations that participants should be informed how to obtain STI treatment for their partners (MRC, 2003) by actually referring partners and volunteers at screening with referral letters to the local clinic, and where possible, providing on-site STI treatment.

Although the ethical principles of justice as equality, reciprocity and beneficence may be used to justify access to HIV prevention interventions for trial participants, guidance remains unclear on the standards of care/prevention for individuals who are not enrolled in the trial (cf. Tarantola et al., 2007). REC interviewees in this study were of the view that there were limited obligations to persons not enrolled in trials and that the provision of such services was morally praiseworthy rather than obligatory.

Previous empirical research has found that in practice trial sites endeavour to provide a variety of services to non-enrolled persons including partners and screen-outs (Ngongo, Priddy, et al., 2012). However, there was some concern that offering services to non-trial participants might constitute an undue inducement and/or make conducting research prohibitively expensive (Ngongo, Priddy, et al., 2012). Similarly, in this study, resource and budget constraints were reported as impeding the provision of HIV prevention interventions to non-trial participants. It has been recommended that researchers and sponsors, in consultation with relevant stakeholders (Tarantola et al., 2007), should determine which services would be provided in trials, the expected beneficiaries of each service, and which services will be made available via referrals (Ngongo, Priddy, et al., 2012).

1.7 Access strategies for ensuring HIV prevention interventions

In practice, access to HIV prevention methods was ensured either via direct on-site provision of services or by referral to private or public healthcare services.

1.7.1 On-site provision of HIV prevention interventions

At all five sites, risk-reduction counselling, male and female condoms and PEP were provided to participants on-site. Four of five sites also provided STI treatment on-site. It was reported by a network representative that the provision of certain services on-site was a requirement:

“...a lot of it’s required and the site needs to be doing it themselves. So counselling we require that the sites are doing it themselves and we do know that that’s happening. When they refer for something like circumcision there are people here at [the network] who are aware of how the sites are handling different issues like that... we require that sites provide condoms and STD treatments” (Z13, network representative).

Another interviewee concurred that certain services should be provided on-site but that others are more appropriately provided via referral:

“I think there’s some things that are just logistically so simple that they should be required of research staff so condoms, you know and the counselling and basic counselling certainly. But things which are more complicated like male circumcision it might be hard to justify making a vaccine trial provide male circumcision services when at the most it might only be used by roughly half your participants, at the absolute most, and there’s a/ it’s a surgical intervention there’s safety issues and other things, and it may in fact be in the participants best interests to be referred” (Z16, REC).

The general position favouring on-site provision of HIV prevention interventions may stem from the benefits of direct provision identified during interviews. Firstly, given the potential for risk-reduction interventions to reduce HIV incidence in the trial and impact on the study design and outcomes, providing prevention interventions on-site was reported to permit better monitoring and control:

“...obviously if the services are provided by the research centres then there’s better/there would be better processes to monitor” (Z22, site staff, site 1).

“I think it’s also wise to treat on-site, because the lifestyle and the wellbeing of a participant, you’ll have a track record. You know, of what has been happening in this particular patient. ...most of them who are coming, they come in for STI treatment. It helps us, for us to know that they’ve been at risk...” (J1, site staff, site 2).

“I think it’s just better to monitor uhm ja it has been given and it has been taken if they do get it on-site” (C9, site staff, site 4).

It was argued that direct provision of prevention interventions facilitates better record-keeping and tracking of participants as opposed to referrals, where follow-up of participants is sometimes difficult, for example:

“...that’s why it’s important for us to actually provide those services on-site because if they’re in a study and you refer them you actually don’t know whether they’re going to go you know until their next visit that they tell you.” (Z17, site staff, site 5).

On-site provision was also reported to facilitate participant retention and permit the efficient delivery of services. Interviewees across most sites referred to the benefit of a “one-stop

shop” where participants could access a multitude of HIV prevention interventions. On-site provision was even argued to result in better data as it allows the development of rapport with participants who in turn are more disclosing of their risky behaviour. Further, having an on-site pharmacy offering a variety of treatments was argued by some to be a basic requirement for a trial site and convenient for participants:

“...this to my mind is a basic prerequisite for prevention studies, that you do provide a one-stop shop... it just makes perfect sense, in terms of a good trial, because obviously it helps for retention, for monitoring participants...” (C11, site staff, site 5)

“...we wanted to have it on-site so that it can really be one-stop for the patients” (Z15, site staff, site 3).

1.7.1.1 Complexities with on-site provision

1.7.1.1.1 Participant dependence on the site

At most sites it was reported that participant dependence on the site was a challenging consequence of direct provision of services, for example:

“So they tend to sort of want [to] depend on the trial site you know. Not really wanting to go to a normal primary healthcare system that is available.” (C3, site staff, site 2).

“I think there’s still a perception on behalf of participants, that they can access total care at a research site...” (C7, site staff, site 4).

“...at times you’ll find out that the participant has STI but it’s difficult for him to go to the local clinic. He will tell you he is not going to get the service, the one expected in the local clinic. It’s better to come here...even if maybe the participant got headache, he will run quickly here.” (Z4, site staff, site 2).

There was some concern expressed that participants may perceive the site as a *“service provider”* rather than as a research centre, which may create challenges because participants are expected to utilise public or private healthcare facilities at the trial’s conclusion.

1.7.1.1.2 Concerns regarding the researchers’ dilemma

Despite several identified benefits of on-site treatment, one argument for ensuring access to prevention services via referral relates to concerns about the researchers’ dilemma or conflicts of interest. However, most interviewees argued that concerns that researchers will dilute prevention efforts in order to increase HIV incidence in trials, by nature of the design

of clinical trials, is a theoretical concern rather than a concern that plays out in actual practice, for example:

“It is a theoretical concern because it goes back to the question of do people understand how we then assess efficacy. ...whatever risk-reduction methods of counselling that we are doing, we do it across the board and we’re all double-blinded...” (Z15, Site staff, site 3).

“I mean I understand the principle. Um, and it’s hard for me to imagine that someone would provide weak counselling and other prevention because they hope the person’s going to get infected, you know, and then we can test the vaccine...I can see it as a hypothetical risk, but it’s hard for me to imagine concretely, how that would actually play out” (C5, REC member).

“...in my experience that dilemma is less problematic at the level of uhm staff working at sites who are/ Because those staff working at sites are obviously blinded and everyone should be blinded to intervention versus control. In fact in my experience in practice staff working at sites want the best for the patients enrolled in their care” (Z16, REC).

1.7.2 Referral for HIV prevention interventions

While direct provision was the preferred option for the provision of most prevention interventions across sites, in select circumstances participants were referred to other healthcare facilities. For the two trials studied here, STI treatment at one site was provided through referral to public healthcare services and VMMC at four sites was provided through referral to private healthcare facilities. Trial sites also used referral as a strategy for ensuring access to STI treatment for participants if an STI remained unresolved after on-site treatment and for ensuring access to prevention interventions for non-trial participants.

In the few circumstances where referrals were utilised, sites made significant efforts to establish relationships with referral centres. In selecting centres for VMMC referrals, interviewees noted that private facilities were more suitable because they were not characterised by long queues and poor provider attitudes described as typical of public sector services (described under complexities below). In addition, private sector providers were reportedly more likely to provide feedback to sites on uptake of services:

“That’s a private facility ja which we’ve arranged. It’s part of his normal activity, daily activities are circumcision work so he’s quite experienced and obviously a specialist and we have an agreement with him that for/ you know if we do have any study participants that require male circumcision that we would arrange that with him. And he has a process of going through it, he has set up tours to explain to them the procedure, and then he makes the appointment for the circumcision, and then he

writes us a feedback letter to say that the circumcision was done on this date and there was no complications, the person's coming back for a follow-up on this date. So it's actually something that makes it easier for us because we know we refer our participants to somebody that understands the requirements for research as well, so we get that bit of paperwork back." (Z17, site staff, site 5).

REC members described certain requirements that need to be satisfied in cases of referral, namely, *“the referral points must be accessible”* (Z12, REC); *“where people are going to be referred uh we expect the researchers to pay the transport”* (C17, REC); and there should be an established relationship with the referral centre:

“...when a research group or a researcher says...in an information sheet ‘you will be referred for treatment’ we want to know where it is and we want a letter from the clinic uh involved to say that they’re prepared to accept the patients because the Americans in particular will um say in studies you will be referred to an appropriate centre, they have no idea where it is, they have no idea whether it’s got the facilities and so on. So we’re quite strict about that.” (C17, REC).

“You know, not just saying, ‘we’re going to refer’, but who are we referring to, and, ja, has this already been negotiated” (C6, REC).

Similarly, interviewees across sites commented on the critical factors to consider in the referral relationship, namely, accessibility of the referral site; monitoring of referral services to ensure quality; and the intricacies of establishing relationships with service providers so as to ensure feedback to sites:

“So we look at whether the participant can access that clinic we are referring to and we write them a letter, send it with the participant to the clinic...” (C8, site staff, site 3).

“But you know for situations where you’ve got to outsource that we then would need to actually come up with ehm you know proposals as to how we can build in monitoring and evaluations of those services so that we ensure that when we’re referring our participants they are going to get good quality you know eh good health quality...as a researcher the issue becomes my responsibility to an extent to check what kind of services are provided you know and whether those are in line with the national department of health eh policies” (Z22, site staff, site 1).

“... I think there’s an understanding, that it’s a joint health service, in many ways... we’ve been very careful not to cultivate the ‘us-and-them’, but really more of, how can we do this together... we need info from them, if our participants go to them because of an adverse event, we need info back, but then it works in the other direction, they need good information from us. ...like any relationship, at the foundation is communication, and also, mutual respect, you know, so we’ve really worked at trying to do that” (C11, site staff, site 5).

Where possible, rather than refer, sites have established partnerships with government to ensure access to prevention interventions on-site, e.g., condom provision and STI treatment. Interviewees across three sites described that in future, they will ensure on-site STI treatment by procuring drugs from the DoH, *ðon the proviso that we supply the stats to them* (C11, site staff, site 5) for example:

“No we don’t get any STI treatment through Department of Health. We’re busy negotiating with them at the moment” (Z17, site staff, site 5).

“We have now signed the Memorandum of Understanding with the Department of Health, and we are going to get supplies as a site so that we can be able to provide that...” (Z15, site staff, site 3).

“...our primary healthcare nurse has managed to work with the government to get the treatment, so instead of us referring people to site where, half the time they don’t get there, and when they get there, you can never guarantee that the counselling that you offer is the same counselling that they offer... we’ve got our interests in these participants and these communities, so the way we treat them will totally be different from a person that’s just offering the service. So what we do in the trials that I work in, is that we offer/ and it has changed like over that/ I think it’s in the past two years that we have started to offer it on-site, rather than to refer.” (Z11, site staff, site 2).

However, it was reported that establishing this relationship was not always easy, for example:

“...And it took us, how many years? I mean [phase IIB trial] was 2006, to 2008, and only now, only last year [2010], we were able to get the drugs from the government to give to STI” (Z11, site staff, site 2).

1.7.2.1 Complexities with referral

1.7.2.1.1 Maintaining confidentiality

Interviewees at some sites expressed concern that maintaining confidentiality of a participant’s health status and trial participation was complicated when participants were referred. Referral to inaccessible centres also increased the likelihood that the participant would be recognisable to staff at the referral centre:

“Because most of the participants still don’t to go to the local clinic just because of the way it’s seen. It’s either a family member working there and you know they don’t want to go there for treatment because then everybody would know.” (Z17, site staff, site 5).

Confidentiality concerns decreased the likelihood that participants would fulfil the referral, for example:

“Maybe you have diagnosed the HIV status or maybe you’re helping them to follow up or for management of some other ailment then it’s important for you to make sure that the confidentiality issue remains or they understand that there’s other people who are going to help them then they need to know more about their health status or their HIV status in that case. So I think confidentiality’s number one issue or problem.” (C3, site staff, site 2).

“...it’s difficult to control or to manage the confidentiality after it leaves you know the trial site. I think that one it creates a bit of a/ I think that’s why participants they feel sort of reluctant to even be referred.” (C8, site staff, site 3).

An interviewee at one site reported that when participants were reluctant to be referred due to confidentiality concerns, they were counselled on the risks and benefits of referral and assured that confidentiality would be maintained at referral sites.

1.7.2.1.2 Long waiting queues

Respondents at all sites reported that a lack of financial and human resources at public healthcare facilities created long queues which deterred participants from accessing services at these facilities. For example:

“...they are a bit reluctant to go or they will tell you about the long list that they are going to have...the long queue that they are going to have to wait for and then as a result they don’t even [go]...” (Z15, site staff, site 3).

“And then now they’ve got to go to the local clinic and they queue, and the risk was that they end up not going there” (Z11, site staff, site 2).

1.7.2.1.3 Poor provider attitudes

Interviewees at some sites said that the value-laden and judgmental attitudes of healthcare providers in the public healthcare sector was a barrier to participant uptake of referrals:

“But normally when they go to local clinic they treat the STI, they are scared to go there because they said they found out the nurses they are too cheeky for them. They ask them ‘last month you were here with an STI, you came back again so we are not going to tolerate this thing.’ So they scared to go there.” (Z4, site staff, site 2).

“But they tell you that at the clinic they are going to be scolded for that... to go to our healthcare facilities...I mean the facilities are there but it’s usually the attitude that everybody/ I think healthcare workers they still have a long way to educate each other regarding their approach, but you always hear everybody say it’s also because they are overworked, they become, they become irritable...” (Z15, site staff, site 3).

“I think when you go to clinics, mostly here, you find that the people, the staff who is working in the clinic is more like older ladies, older guys, so when the participant comes or when the patient or the community member comes and picks up a box of

condoms, there's always remarks, you know, they always say something. So with us, we try to make them feel at home, so they prefer to come to us.” (Z8, site staff, site 4).

1.7.2.1.4 No feedback from referral centres

Interviewees at some sites described that the feedback loop between referral centres and trial sites was poor and that site staff had to actively engage with the referral clinic to get feedback on participants:

R: So you don't get the feedback from that referral clinic?

C8: No. Ja until you follow it up and want to find out from the participant maybe to say “did you receive this” after maybe the participant has gone to the clinic then you phone again and find out to say “how did it go, did you receive any help after that”. Otherwise they normally don't send us the feedback. (C8, site staff, site 3).

“...we always ask...whoever we are referring to, to provide feedback to us and I think one challenge has been we normally don't receive any responses or feedback from the referral clinic” (C3, site staff, site 2).

“...to get information from that healthcare provider is extremely challenging” (C7, site staff, site 4).

1.7.3 Comparing access strategies for providing prevention interventions with recommendations in ethics guidelines

Guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) specify that researchers and sponsors should ensure access to prevention services for trial participants but allow some flexibility by not specifying which HIV prevention interventions should be provided on-site and which should be accessed via referrals.

But for a few exceptions, most HIV prevention interventions for trial participants were provided on-site. The challenges identified with referral above created barriers to the use of referral as an access strategy for the standard of prevention. Given the potential of HIV prevention interventions to impact on HIV incidence, on-site provision of services helped site staff to maintain better control. Similar challenges with referral have been identified elsewhere and it has been noted that simply referring participants to available services was inadequate in that often they did not fulfil the referral (Heise et al., 2008; Ngongo, Priddy, et al., 2012).

In line with guideline requirements, where referral networks were established, sites endeavoured to ensure referral uptake by following up with participants or by linking with referral centres to ensure feedback to sites.

Some sites reported that they had created partnerships with government where the DoH provided the treatment at no cost to sites and the site was able to provide the prevention service on-site, thus increasing the ability to monitor quality and uptake of services and improve participant retention.

1.8 Comparing monitoring practices for the standard of prevention with recommendations in ethics guidelines

Ethics guidelines recommend that the provision of risk-reduction interventions be monitored for quality (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) and uptake (UNAIDS/AVAC, 2011), including the standards of referral services (UNAIDS/AVAC, 2011, p. 51).

Mechanisms for monitoring risk-reduction interventions were not addressed in the protocol or accompanying documents. However, the risk-reduction worksheet that captured the counselling session and condom provision was reviewed by counselling mentors. Further, at some sites the provision of risk-reduction counselling was monitored for quality:

“...what my role, I’ve got a, I think it’s a checklist where I used to sit down with the counsellors to see their chart-notes. To see that ok so much condoms have been issued.” (Z2, site staff, site 1).

Many reported practices could reflect monitoring activities such as recording condoms dispensed, recording STIs and their resolution, and recording uptake of PEP and VMMC. The uptake of individual components of the standard of prevention package is collated in participants’ records.

Interviewees at some sites reported that there were no formal mechanisms for monitoring the quality of risk-reduction interventions. However, guidelines (MRC, 2003; UNAIDS/WHO, 2012) do not explain what they mean by monitoring the quality of risk-reduction interventions, and except for counselling, it is unclear how the quality of these prevention services should be measured or monitored.

While some interviewees described the importance of monitoring referral networks, no formal monitoring mechanisms of referral networks were reported. Ngongo, Priddy, et al. (2012, p. 1286) found that in certain contexts, “formal assessment of quality of referral points in general is rare”. However, most prevention interventions were provided on-site and referral was a limited strategy reserved for the provision of select prevention services, suggesting that monitoring of referral centres was not a necessary priority in most settings.

2. Summary

This chapter addressed the research question of the extent to which actual HIV prevention practices in HVTs corresponded with related recommendations in ethics guidelines and to identify complexities with implementation. All ethics guidelines require that participants be ensured access to a comprehensive package of HIV prevention interventions, described as “state-of-the-art” (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) or “optimal” (MRC, 2003). The HVTs in the present study satisfied these ethics recommendations by providing risk-reduction counselling, and access to male and female condoms, STI treatment (cf. MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), and VMMC and PEP, where indicated (cf. UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

Several complexities were identified with meeting ethics guideline requirements to provide an optimal or state-of-the-art prevention package. Most complexities can be clustered at four major thematic levels, namely (1) partnerships/funding; (2) provider-promotion; (3) participant acceptability and uptake, and (4) cultural/gender norms (discussed in Chapter 11). The next chapter presents stakeholders’ perspectives on selected standard of prevention recommendations in ethics guidelines.

CHAPTER 10

PERSPECTIVES ON STANDARD OF PREVENTION RECOMMENDATIONS IN ETHICS GUIDELINES

This chapter presents respondents' perspectives on selected standard of prevention recommendations in ethics guidelines. Respondents were asked about their perspectives on the utility of ethics guidelines in addressing ethical complexities. They were also asked to comment on specific standard of prevention recommendations in UNAIDS/WHO (2012) guidelines, namely, that 1) access to all state-of-the-art HIV risk-reduction methods should be ensured for participants; 2) new tools should be added to the package based on consultation among all research stakeholders; and 3) trials should not be conducted when agreements have not been reached among all research stakeholders on the standard of prevention. These particular recommendations were selected because they have been identified as potentially divisive (Essack, Slack, et al., 2010; Philpott et al., 2011), and as requiring further in-depth exploration (Moorhouse et al., 2014).

1. Awareness of ethics guidelines

One of the key identified obstacles to the implementation of recommendations in ethics guidelines was a lack of accessibility, awareness and understanding of these guidelines, even among REC members:

"...we are not educating our committee members, you know we're falling very short there. You know, we're busy educating everybody else, (laughs) but not locally, and unless you're familiar with the UNAIDS guidelines, you don't know what is expected really" (C6, REC).

Some key stakeholders, including communities, reportedly had no mechanisms to access ethics guidelines nor were they aware of specific guideline requirements for HVTs:

"I think as a community person and also the community representative on staff, I don't think we as the community understand those guidelines... there's no document that is available to the community to say [these] are the guidelines of the prevention and all those things" (Z2, site staff, site 1).

Even when guidelines were accessible, without accompanying awareness and understanding of what guidelines entail, it is unlikely that ethics recommendations will be consciously implemented in trials. Therefore, there is a need for more "...training about ethical standards [and] policies" given that at present "there is no time to absorb them and make them a

reality thingö (C1, site staff, site 1).

2. The value of ethics guidelines

One of the key purposes of ethics guidelines is to offer stakeholders sound direction on current ethical complexities (Moorhouse et al., 2014). To this end, MRC (2003) guidelines were developed to provide information, and some resolution, on key ethical challenges and dilemmas. Similarly, UNAIDS/WHO (2012) guidelines purport to capture some of the critical ethical elements for consideration during the development of biomedical HIV prevention interventions and GPP guidelines (UNAIDS/AVAC, 2011) aim to provide systematic guidance on effective stakeholder engagement during HIV prevention trials.

A few respondents reported that they did not consult UNAIDS guidelines at all regarding standards of prevention. Rather, they argued that their practices were based on sound clinical judgements and the application of ethics principles. Another potential reason for the lack of reference to these guidelines may be because they were not formally endorsed nationally or by the implementerø respective institutions (cf. Haire, 2013).

Among those who perceived guidelines as valuable, different aspects of the guidelines were reported as having appeal. In line with guidelinesø(MRC, 2003; UNAIDS/WHO, 2012) aims to offer comprehensive guidance on critical ethical elements, some respondents stated that guidelines provided a valuable benchmark against which to compare actual practices in HVTs, for example:

“...because that’s what really guides us even in general when looking at the protocol, to say is it going to provide the participants what the guidelines say I need to provide to participants? I do agree that it’s been very helpful.” (Z15, site staff, site 3).

While acknowledging that guidelines are not mandatory or binding, and therefore not enforceable, another respondent stated that guidelines served to regulate research, albeit implicitly, in terms of their ratification of ethical standards for research:

“I think it’s absolutely necessary that you have the guidelines. It may appear to be a nuisance, or it may appear to be of no consequence. But, it is there, for want of a better word, [as] a watchdog in place.” (Z10, site staff, site 5).

However, guidelines were perceived as less valuable as stand-alone documents ó rather they were seen as providing helpful direction relative to other considerations when balancing competing ethical obligations. The importance of value-judgments were emphasised in the

caveat that the ethicality of guidelines cannot merely be assumed by virtue of being guidelines nor can a recommendation be argued as valid just because it is stipulated in guidelines: *“I don’t think you can simply point to a guideline, and say, it must be true or it must be ethical because this guideline says it is”* (C5, REC).

3. Perspectives on UNAIDS ethics recommendations

As indicated in Chapters 3 and 5, standard of prevention recommendations in UNAIDS/WHO (2012) guidelines have been the source of intense debate. Among the concerns raised are that standard of prevention norms are infeasible and impractical (HPTN, 2009), and set a very high standard (Essack, Slack, et al., 2010; Macklin, 2009). Some respondents concurred that UNAIDS recommendations have *“upped the ante in terms of the requirements of research...and are making, quite a lot of demands on researchers”* (C6, REC). The dissimilarity between UNAIDS/WHO (2012) guideline recommendations and the arguably more pragmatic HPTN (2009) guidelines was also noted. While recommendations in UNAIDS guidelines were considered *“unrealistic”*, it was argued that, *“that doesn’t mean to say that one mustn’t again aspire, I suppose that’s what ethics is about. But the HPTN ones, I think are a bit more realistic....”* (C6, REC).

Respondents were asked to specifically reflect on selected standard of prevention norms in UNAIDS/WHO (2012) guidelines, as detailed below.

3.1 Perspectives on the state-of-the-art requirement

3.1.1 Support for state-of-the-art prevention

Despite the criticisms identified in the literature, there was some support for the provision of state-of-the-art HIV risk-reduction interventions for HVT participants:

“Yes they must be given the best prevention ever.” (Z1, CAB, site 1)

“I think it’s quite right [that participants are offered state-of-the-art prevention interventions]” (Z19, CAB, site 4).

“...the participants have to have the best choice offered to them” (Z10, site staff, site 5).

“I think that’s entirely appropriate...” (C19, REC).

As indicated from the quotes above, respondents tended to interpret state-of-the-art

prevention as the best available prevention strategies.

The state-of-the-art standard was also perceived by a few respondents as easily implementable and affordable:

“...it’s very easy for a site to do so” (Z19, CAB, site 4).

“...in the context of South Africa, we’re slightly different from other African countries, I think here, that standard of care is affordable” (Z12, REC).

3.1.2 Complexities with state-of-the-art prevention

3.1.2.1 State-of-the-art is an undue inducement

While CAB respondents largely advocated for the provision of a state-of-the-art standard of prevention for participants, one CAB member argued that to do so would be unfair and would raise concerns about undue inducement (see Chapter 8).

3.1.2.2 State-of-the-art is vague

While guidelines establish the substantive standard of state-of-the-art (UNAIDS/WHO, 2012), defining this standard is a task left to the reader. It is therefore concerning that several respondents in this study reported that the state-of-the-art requirement is unclear and too vague:

“...I think it’s a very vague ethical recommendation ... it needs more clarification.” (C21, REC).

“...there’s just a minor problem with that requirement, because half the time it’s difficult to define the standard” (Z11, site staff, site 2).

“...state-of-the-art, um, makes me more uncomfortable than ‘optimal’ treatment (laughs). Um, because it seems fuzzier.... Thinking about prevention, what would state-of-the-art prevention be?...I find it harder to have a clear opinion or to imagine coming up with what state-of-the-art would be, and ...to what degree you would require it.” (C5, REC).

This vagueness also renders the state-of-the-art recommendation open to multiple interpretations, potentially polarised by the interests of different stakeholder groups, for example:

“...state-of-the-art is in the eye of the beholder and ...may vary between scientists and stakeholder groups and may vary within stakeholder groups certainly and so I

suppose it's a potential concern that some stakeholders may define a different state-of-the-art than others." (Z16, REC).

"The researchers would say 'you are crazy. I mean what are you expecting of us?' The community would grab it because it's good care for them" (C6, REC).

While acknowledging that it is difficult to operationalise vague guidelines, a few respondents argued that vagueness may be warranted because it allows some latitude in interpretation, suitable to the dynamic nature of the HIV prevention field:

"...it's for us to unpack what that state-of-the-art is" (Z15, site staff, site 3).

"I think that's entirely appropriate and I think they are necessarily vague because the landscape is changing...but the vagueness also I suppose creates problems about what is sufficient and what is state-of-the-art and so it's a catch 22" (C19, REC).

"So, you know, I think it's a very dynamic field and it needs ongoing dialogue, and it's gonna change so frequently that I think we should be careful not to, you know, um, spend hours coming up with guidelines which then need to be changed within a month, and then we're reluctant to be flexible and dynamic because we've put so many hours into them" (Z18, site staff, site 5).

Vagueness was argued to be valuable because it provides welcomed reprieve from guidelines which were perceived as too rigid and therefore likely to be ignored:

"I don't think you could remove the flexibility because people then won't adhere to the guidelines, which I think is a problem with Helsinki. It is too rigid in some respects so you end up ignoring the guideline because it is ridiculous." (C6, REC).

However, one respondent did perceive that rather than flexible, the state-of-the-art requirement was too rigid:

"...the problem with those kind of unanimous blanket statements is there's always the ridiculous outlier scenario... I don't know what's coming down the pipe, so I'd rather keep my options open." (Z18, site staff, site 5).

While there was little consensus on exactly what constitutes state-of-the-art, the prevention package provided to participants in the phase IIB trial was considered, at the time, "a comprehensive state-of-the-art package" (C19, REC).

3.1.2.3 State-of-the-art sets the bar too high

Another criticism was that the state-of-the-art requirement sets the bar too high and therefore is an unrealistic, unreasonable, and "very limiting" standard (Z5, site staff, site 2).

“I don’t think that it’s reasonable to require that the best form of every kind of prevention be available to everybody, all the time” (C5, REC).

In this way, the state-of-the-art standard was perceived as not feasibly implementable under all circumstances. In resonance, recent research on care and prevention recommendations in ethics guidelines (Moorhouse et al., 2014) found that South African stakeholders rated standard of prevention norms in UNAIDS/WHO (2012) and GPP (UNAIDS/AVAC, 2011) guidelines lower than care norms in terms of familiarity, understanding and implementability. REC respondents in particular were more sceptical of trial sites’ abilities to implement these prevention norms (Moorhouse et al., 2014).

Despite concerns that state-of-the-art is infeasible and impractical (see also HPTN, 2009), it was acknowledged that this high standard has actually been achieved in HVTs:

“....To me they are probably too absolute, and they are too high. But having said that, again, your sites that are doing these studies and are actually meeting these requirements. So, from our perspective where I’m sitting it is less of a problem because they are doing it. In less well-resourced sites, it may be possible to not do the study at all because it’s almost self-defeating. So, I’m probably, you know, sitting... with well-resourced sites. I’m not able to give the best answer, because I think it’s happening, I think/ and the researchers are good. Whether it’s possible to enforce, without cutting off your own nose, I don’t know.” (C6, REC).

3.1.2.4 State-of-the-art needs localisation

Many respondents contended that a state-of-the-art package customised to the local setting is preferable, for example:

“...obviously because one has to consider the context... so the state-of-the-art would be whatever the national guidelines are” (C21, REC).

“I think that it’s true, they should be provided with everything but then you also have to look at your, the context of uh you know your settings... You provide it as far as possible but if it’s not feasible in your setting, then you can’t really do it.” (Z7, site staff, site 1).

“Many of these studies are done in the global world, and what may be appropriate for Brazil, may not be appropriate for a site in Gugulethu...the world is not the same place, all over the place. Um, and I think we need to be careful that having a blanket statement that could actually cause more harm than good” (Z18, site staff, site 5).

“...what is considered state-of-the-art in in the in the States is obviously different from state-of-the-art in Africa...” (C21, REC).

While several respondents argued that the standard of prevention should be benchmarked

against the public healthcare sector, there was some uncertainty about whether the prevention package offered in the South African public health system would be considered state-of-the-art and which level of localisation (e.g., national, provincial, metropolis) would be most appropriate:

“So it just gets into the grey area that I’m never sure about which is what’s state-of-the-art versus what’s standard of care... but I don’t know that it needs to be the responsibility of the trial to provide a service that’s not in fact a public sector service.” (Z16, REC).

“I think we have to take the local context into consideration but sure there would be a tension between state-of-the-art versus sort of a customised state-of-the-art.” (Z13, network representative).

“So, the [state-of-the-art] standard is also situational based, and what is standard in KZN may not be standard in Soweto. And, so, the first problem with that clause is, what’s the standard?” (Z11, site staff, site 2).

It was argued that the standard of prevention implemented in developed country contexts should not be imposed on developing contexts, where it is unlikely to be feasible. Even within one context, there may be differences in public health practice. Given potential socio-cultural and economic idiosyncrasies of each context, a one-size-fits-all approach was perceived as encumbering implementation. Instead, a customised prevention package would demand that the state-of-the-art standard is dictated by local realities, always implementable, and does not impact on the real world significance of the data. However, it was cautioned that a customised prevention package runs the risk that the package may be suboptimal in some contexts:

“...it also does allow for some accommodation to what is feasible locally, provided that that’s not just nothing.” (C19, REC).

Another benefit of defining state-of-the-art in relation to the national standard of prevention was that it would enable establishing a fixed standard *“for a South African setting for instance...it would be very simple, just mandate that that standard of care be provided to all participants.” (Z16, REC).*

It has been argued that the procedural standard (UNAIDS/WHO, 2012) requiring consultation and negotiation among all research stakeholders on the standard of prevention, permits such customisation (Macklin, 2009). However, this supposition appears discordant with the view that the primary intention of the UNAIDS guidelines is to avoid double-standards between

high- and middle- or low-income countries, and serve as a tool in the progressive realisation of the right to health (Haire et al., 2013, p. 3). Rather, a customised standard of prevention appears to fit well within the HPTN guidelines, which through their adoption of a social justice perspective, aim to minimise double standards between trial participants and their local communities.

3.2 Perspectives on the stakeholder consultation requirement

3.2.1 Support for consultation and consensus among research stakeholders

Several respondents, particularly CAB representatives, supported the idea that new prevention interventions should be added to the prevention package based on consultation among research stakeholders:

“...the involvement of all stakeholders. I think it is essential. It’s not just important but it is the core” (Z3, CAB, site 2).

“It’s something that’s difficult but it’s something that needs to be put into practice. I think it’s something that needs to happen” (Z11, site staff, site 2).

“I think it’s a very good requirement because everybody must agree with the same thing” (Z19, CAB, site 4).

“I think it’s a sound recommendation” (C14, network representative).

A few respondents identified the rationale for, and benefits of, stakeholder consultation. The ethical principle of respect for communities was perceived as justifying stakeholder consultation on standards of prevention. Such consultation was identified as serving several purposes including fostering community ownership of the research and meeting the community’s desire to be involved in decisions that affect it. For example:

“...it’s very good to involve everyone, it respects the notion, and the principle of community engagement” (Z12, REC).

“...gone are the days when people just used to take and swallow what they are given. People want to be involved from the plannery stage...” (Z3, CAB, site 2).

“...it’s very important because like I said communities are not the way they used to be before, you know they know their rights, so you need to explain to them what’s going to be conducted in their area, so you need to get their permission also. So I think it’s actually very important to engage stakeholders because they are the activist, they are the people who are advocating on behalf of the community” (Z8, site staff, site 3).

Community mobilisation and engagement were considered critical for fostering buy-in and

community ownership of research whereas a failure to engage communities was argued to be detrimental to research:

“...[when communities are engaged] we’ll provide that little pondokkie¹² as our counselling room for the person that’s going/ because now they all are involved and they can relate and identify with the thing [research]. Yet if you just come upon them and force it down their throats, it’s not going to work” (Z3, CAB, site 2).

Consultation was also argued to promote ethical research in that it serves an oversight or watchdog function (J1, site staff, site 2). However, among those respondents who supported stakeholder engagement, few specified the finer decision-making required by ethics guidelines for standards of prevention. Most perceived this ethical recommendation as synonymous with broad community engagement, consultation and mobilisation.

3.2.2 Complexities with consultation and consensus among research stakeholders on the standard of prevention

Even when the idea of consultation and consensus was deemed sound and feasible, several respondents went on to qualify their support (see below), and most respondents were critical of the recommendation for stakeholder consultation on the standard of prevention.

3.2.2.1 Questioning research stakeholders

Ethics guidelines (UNAIDS/WHO, 2012, p.45) specify that decisions on the addition of new tools to the prevention package should be made in consultation with all research stakeholders, including the community. Since these guidelines do not expand on who is considered a research stakeholder, this recommendation was perceived as equivocal. Respondents questioned which specific stakeholder groups should be included in standard of prevention determinations. While vagueness may be argued to ensure generic applicability depending on circumstances (Macklin, 2012), some respondents questioned the lack of specificity. For example:

“...it says all the research stakeholders, and I think it’s [not] all the research stakeholders that play a part. It’s only the people that play part that really must be part of that.” (Z11, site staff, site 2).

“I’m not sure who are regarded as the stakeholders” (Z18, site staff, site 5)

¹² Pondokkie is a colloquial term for small room/house.

“...it’s an open point of whom are you going to consider as a stakeholder” (C16, site staff, site 3).

“The question is going to be really when you say stakeholders, we have to unpack that. We have to unpack it because most of the time who are we really referring to as stakeholders?” (Z15, site staff, site 3).

Even when the recommendations of consultation and consensus were endorsed by respondents, it was done under the proviso that only relevant stakeholders should be consulted, as aptly indicated by the retraction from *“everyone”* to *“all the important stakeholders”* in the quote below:

*“...it is crucial to make sure that **everyone, eh eh all the important stakeholders** reach an agreement as to okay this is the package that needs to be provided” (Z22, site staff, site 1, emphasis added).*

Some respondents attempted to delineate those stakeholders they considered relevant. These stakeholders were limited to investigators, sponsors and RECs, with some also considering CABs as valuable stakeholders to be included in standard of prevention determinations. However, while some argued that such involvement was considered feasible in terms of the current CAB model, others contended that the CAB model was inadequate for ensuring community representativity in decision-making. There was also some scepticism about whether CABs are actually involved in such intricate decision-making such as on standards of prevention:

“Um off the top of my head I would say that although studies are typically asked to provide an indication that the community support and agree with the study I’m not sure that the CAB or the community representatives necessarily comment on detail as fine as the standard of care that’s gonna be provided” (C19, REC).

Analogously, some CAB respondents in this study reported having made limited inputs on standard of prevention decisions in practice and for some, the standard of prevention was not highly prioritised (see Chapter 7). A lack of scientific expertise was noted to potentially impede CAB review of standards of prevention in protocols. Similarly, it could be argued that this paucity of scientific knowledge among CAB members does not bode well for the negotiation of technical study design considerations such as feasibility, expected impact, and the ability to isolate the efficacy of the biomedical HIV modality being tested - all of which are required to be considered during stakeholder negotiations (UNAIDS/WHO, 2012). A community liaison officer also questioned the value that CABs would contribute to such technical decision-making:

“...let’s take for the scientific working group, they are all doctors, they understand what are they talking about. And these people, maybe this community, maybe it’s a teacher or it’s somebody who hasn’t any understanding of the science whatsoever.” (Z2, site staff, site 1).

A more restricted view of who would constitute a research stakeholder was also held by some respondents who cautioned against affording too many stakeholders the opportunity to participate in decision-making:

“I would hate to give you know um too many voices the opportunity to participate in the discussion because it may be a never ending discussion and could change from time to time.” (C20, REC).

“Well I think you know it’s quite a lot of stakeholders involved in the protocols but it should be the ones that actually going to have to provide it that definitely need to agree on what should be there and all that should be accessible to participants.” (Z17, site staff, site 5).

As with state-of-the-art, vague recommendations run the risk of being open to multiple interpretations. While the need to maintain flexibility in guidelines is acknowledged, implementers would benefit from frameworks that provide more concrete direction. For example, Tarantola et al. (2007) provide an exhaustive list of all research stakeholders which may be of value when determining who should be involved in standard of prevention determinations and GPP guidelines (UNAIDS/AVAC, 2011) also explicate the relevant stakeholders in HIV prevention trials.

3.2.2.2 Questioning the consultation process

While consultation and negotiation are advocated in guidelines (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), the process for consultation is not specified (Cohen et al., 2014; Philpott et al., 2011), and left to the discretion of implementers. Therefore, there is likely to be *“enormous variation in the way it’s operationalised”* (C19, REC).

Respondents defined consultation differently. Some understood consultation to mean one-way communication or information sharing: *“everybody needs to know what’s going to be available”* (Z17, site staff, site 5) and *“everybody has the right to be informed”* (Z10, site staff, site 5). However, most respondents equated consultation with face-to-face meetings. The value of large consultative forums was questioned, particularly with regard to investments of time and resources, and the pragmatics of power between stakeholders. For example:

“...I tend to...be sceptical of these kind of, consultation processes... these kind of things seem naive to me because it imagines that if we’re all in the room and we start from square one then there won’t be any power, there won’t be any ignorance, there won’t be any, you know, conflict” (C5, REC).

“I guess I’m a bit sceptical about meetings generally because... I think there would be a problem practically getting people together. I mean government people rarely turn up for meetings. There’s quite a high opportunity cost of people’s time, and I guess I wouldn’t support that too easily” (C6, REC).

“There’s a time and a complexity concern obviously...” (Z12, REC)

“Of course, what you mean by consultation, you know you have to, give people plenty of time, you have to help them understand what the other options are, and then, why yours are the best. That’s different than just having them show up and giving PowerPoint and saying, ‘Do you agree?’” (C6, REC).

The manner in which consultations are conceptualised has obvious implications for the implementability of this ethical recommendation. Some respondents deemed protocol development and review to serve as an adequate consultative device:

R: Uhm do you think that consultation happens in other ways beside perhaps meetings or direct discussions in the sense that CABs may get to review the protocol, RECs review the protocol. Do you think that this may be considered by sites as in some sense, consultation?

Z6: I do and it probably happens at other levels as well but uhm uh yeah I mean I don’t think that necessarily the absence of a formal ‘ok today we’re having a meeting to discuss standard of care before we start trial X’ uhm the absence of that type of meeting means the absence of consideration of the issues on an ongoing basis (Z6, site staff, site 2).

“...at the moment our PI’s are having to consult communities. I guess, you know, the criticism is it’s after the fact. You know, you’re presenting them with a protocol. You know, you’re not going in and saying let’s develop a protocol, which I think does have very practical problems. So if they agree to it, you have/ you can tick that box. The same with the MCC, the same with the ethics committee...I would stay that is a reasonable standard of consensus...you know, having meetings would be, I think a huge investment of time, and not necessarily productive time/ you know if it can be done separately. Because already, I think that trying to get through many of these processes is quite a task.” (C6, REC)

“I think that’s one method of consultation, protocol review... that protocol document, you know, goes through the protocol development process, and then it’s reviewed by local ethical bodies, and national ethical bodies, so, um, that’s another form of consultation” (Z9, network representative).

The requirement for stakeholder consultation was perceived by some as too demanding (*“quite a task”*) and vague (*“would it be each country, would it be continental?”*; *“it’s difficult to define the standard”*).

3.2.2.3 Questioning consensus

Some respondents also critiqued the recommendation that consensus be reached on the standard of prevention prior to every trial (UNAIDS/WHO, 2012).

It was noted that consensus is difficult to achieve and an unlikely outcome of consultation on the standard of prevention, which is an issue already marred by debate:

“... I don’t think you can kind of bring everyone together and hope that they will, from the bottom up, produce something that’s, kind of, shared... it would make sense to develop a package, and motivate for it, and then, properly get people involved and get them to sign off on it” (C5, REC).

“...there’s a difference between consensus and unanimity. And (.) I think that, it’s very good to involve everyone, it respects the notion, and the principle of community engagement, but at the end of the day you’ll find/in my opinion there doesn’t need to be unanimity on the issue. There just needs to be consensus. So even if some of the stakeholders disagree, to anything, whether it’s study design or whether it’s whatever, the bottom line is that, as long as most of the stakeholders are in general agreement (R: Mm), then, at the end of the day there’s consensus.” (Z12, REC).

“I think that’s uh being rather fanciful...I think to say that you have to get absolute agreement is, would be a major barrier.” (C18, site staff, site 4).

I’m a little hesitant to say that we have to reach consensus across the board or we can’t do this study.” (Z18, site staff, site 5).

Given that stakeholders have varying perspectives and are driven by their own self-interests, the recommendation for stakeholder agreement was argued as being *“to the detriment of the participants and maybe even to doing vaccine trials”* (C4, site staff, site 2). As evidenced by varying perspectives both within and across stakeholder groups in this study, and the perspective that *“state-of-the-art is in the eye of the beholder”* (Z16, REC), it follows that it may be problematic to require agreement on an issue for which there are many opposing perspectives.

Still others argued that the requirement for stakeholder agreement in itself is not situated in the reality that under certain circumstances, disagreements best serve active decision-making. Disagreements may in fact indicate that procedural justice is working (Ashcroft, 2008).

Consensus, on the other hand, may be achieved for a variety of reasons including skewed power dynamics and passive compliance merely to reach resolution. For example:

“Because sometimes we agree to disagree. And there are healthy disagreements, which can make the trial...there are those agreements, sometimes we agree, but is it because we agree, or is it because sometimes we get too tired to disagree...For me it would be healthy, even if we disagree. Because disagreeing, sometimes takes us somewhere” (Z11, site staff, site 2).

The recommendation that consensus should be achieved prior to the commencement of every trial was also not favourably received, considered infeasible and unlikely to be implemented:

“Uhm in the sense that we’re part of an iterative process, it’s a bit unlikely that that’s gonna happen. You know it’s not like we’ve landed from Mars and we’re confronting a problem that is unique to Mars and we have one intervention and we’re going to see if it works in one trial. The whole vaccine development process has been going on for 20 years. So in the sense that each trial needs to confront this every time a new trial is done, uhm I think is unlikely to uhm to really take off in my view” (Z6, site staff, site 2).

The analogy of an alien landing may indicate the extent to which this recommendation was considered incredulous. During the introductory consultation with HVT stakeholders in this study, it was reported that since HVTs are ongoing processes, decisions on what to include in the prevention package are rarely established through dialogue and it may not be feasible to have consensus debates on the standard of prevention for every trial (Essack, Koen & Slack, 2009).

One proposal was that instead of endeavouring to achieve consensus on the standard of prevention for every trial, it would be more worthwhile to consult stakeholders only when the proposed prevention package deviates from the normative standard or accepted practice.

4. Summary

This chapter addressed the research question of what are the perspectives of HVT stakeholders on selected norms in ethics guidelines. These norms in UNAIDS/WHO (2012) guidelines have been identified as controversial (Essack, Slack, et al., 2010; Haire et al., 2013; HPTN, 2009; Philpott et al., 2011), including those specifying that participants should get access to state-of-the-art prevention interventions; that new tools should be added based on consultation among all research stakeholders, including the community; and that trials should not be conducted unless agreement is reached among all research stakeholders on the standard of prevention.

Respondents were asked to share their perspectives on these particular ethical norms. While there was modest support for these ethics recommendations, most respondents identified several complexities. The 'state-of-the-art' recommendation was considered too vague, too absolute and as requiring localisation. The consultation requirement was questioned in terms of who would constitute relevant stakeholders, the challenges of achieving consensus, and the nature and composition of the consultation process.

The procedural recommendation of stakeholder consultation on the standard of prevention, opens the state-of-the-art standard to negotiation. Respondents in this study questioned which stakeholders should be included in such decisions. By opening the normative standard for negotiation, there is also potential to undercut the state-of-the-art norm, and thus lower the prevention package (Essack, Slack, et al., 2010; Haire et al., 2013).

CHAPTER 11

DISCUSSION

In the preceding results chapters (Chapters 7-10), specific findings were discussed in relation to ethics guidelines and literature. Chapter 7 presented empirical data on the key dimensions of standard of prevention decision-making. It explored perspectives on why participants should receive access to prevention interventions in HVTs; which stakeholders were involved in standard of prevention decision-making and their roles; how decisions were made and at which time-points (the decision-making processes); and the related complexities experienced by stakeholders. Correspondence with norms in ethics guidelines was evaluated for each of these dimensions. Key findings included that there was little consensus on the ethical rationale for providing prevention interventions to trial participants. The various justifications offered by respondents closely resembled those declared in ethics guidelines and identified in the literature. However, respondents in this study identified mitigating community mistrust of research as an additional rationale for providing prevention interventions to participants. In practice, the protocol development committee emerged as the primary decision-making body for the standard of prevention. RECs and CABs did not entirely satisfy their standard of prevention review responsibilities outlined in ethics guidelines, focusing more on procedural rather than substantive ethical issues. Practices deviated from guidelines with regard to the declaration of the standard of prevention in ICFs and protocols. Key identified complexities included sponsor funding policy, REC and CAB capacity deficiencies, and the presence of power inequalities at various stages of decision-making.

Chapter 8 presented stakeholders' practices and perspectives on the evolving standard of prevention. It explored how stakeholders made the decision to add VMMC to the prevention package and their perspectives on the relevant criteria for adding new tools to the standard of prevention. Practices and perspectives were compared with norms in ethics guidelines. Perceived challenges with the evolving standard of prevention were described, and guidelines were examined to identify whether they anticipated these real-world concerns. Findings indicated that respondents endorsed ethics guideline recommendations that new tools should be scientifically validated although they argued that this broad concept is difficult to operationalise; respondents also generally subscribed to the more conservative interpretation of guidelines that new tools should be approved by national regulators in the host country

before being added to the standard of prevention. In addition, there was some support that new prevention methods should be available in the public healthcare sector and that determinations on what to provide should consider the phase of the trial/risk level of participants. However, in practice, VMMC was added to the package when it was scientifically validated but not necessarily endorsed by national bodies for use. The evolving standard of prevention was perceived as particularly contentious and respondents raised the usual concerns reflecting tensions between 1) science and ethics; 2) ethics and pragmatics of cost; and 3) protecting participants versus creating undue inducements and inequities between participants and their communities. In addition, they raised concerns that new partially effective prevention interventions may undermine existing, efficacious interventions.

In Chapter 9, standard of prevention implementation practices and perspectives were examined for trial participants and other morally relevant groups (participants/partners, families and the wider community) vis-à-vis ethics recommendations. Complexities with implementing standards of prevention in HVTs were also identified. Despite the complexities identified at the level of decision-making, many site practices for standards of prevention could reflect ethics guideline recommendations. Trial participants were provided with risk-reduction counselling and access to male and female condoms, STI treatment, as well as VMMC and PEP, where indicated. Several complexities were identified with meeting ethics guideline requirements to provide an optimal or state-of-the-art prevention package – these can be broadly clustered at four major thematic levels, namely, partnerships/funding, provider-promotion; participant acceptability and uptake; and cultural/gender norms.

Chapter 10 presented stakeholders' perspectives on selected standard of prevention norms in ethics guidelines, namely, that participants should get access to state-of-the-art prevention interventions; that new tools should be added based on consultation among all research stakeholders, including the community; and that trials should not be conducted unless agreement is reached among all research stakeholders on the standard of prevention. While there was modest support for these ethical recommendations, most respondents identified several complexities. The state-of-the-art recommendation was considered too vague, too absolute and as requiring localisation. The consultation requirement was also questioned in terms of who would constitute relevant stakeholders, the challenges of achieving consensus, and the nature and composition of the consultation process.

This discussion chapter attempts to identify and relate the underlying ideas or assumptions (latent themes) (Braun & Clarke, 2006) in respondents' reports of their practices and perspectives on the standard of prevention to the literature and normative frameworks. This chapter aims to move beyond a descriptive analysis of the results by offering an explanation and interpretation of the study's key findings. It ends by reflecting on the study limitations and the role of the researcher in the research process (reflexivity).

Key complexities identified by respondents are clustered thematically into four overarching themes, namely: 1) dynamics of standard of prevention decision-making and implementation; 2) defining the standard of prevention through consultation, consensus and negotiation; 3) ensuring access to HIV prevention interventions; and 4) double standards of prevention.

1. The dynamics of standard of prevention determinations and implementation

1.1 The impact of culture

This study found that cultural taboos impeded CAB discussions on the standard of prevention. Many of the communities where HVTs are conducted are permeated by established cultural mores and values where sex is considered a taboo subject (Ndinda, Uzodike, Chimbwete & Mgeyane, 2011). Such taboos may also be ingrained due to politico-legal prohibitions during apartheid, where issues of sex and sexuality were highly censored and subjected to repressive policing (Posel, 2004). Further, there is increasing recognition of the role of culture in HIV prevention (Leclerc-Madlala, Simbayi & Cloete, 2009).

Previous research in a South African rural community revealed that sex is a taboo subject and its discussion is obscured by the use of polite language, euphemisms, and gestures (Ndinda et al., 2011). Further, discussions related to sex are gendered (Ndinda et al., 2011). While counter-intuitive given their involvement in HVTs, some CAB respondents in this study reported that their standard of prevention discussions were constrained by cultural taboos. As with some CAB respondents in this study, men from particular ethnic groups may exhibit significant levels of anxiety in discussing private sex matters in the presence of women (Ndinda et al., 2011, p. 4). For some CABs, the proscription on discussing sex in a mixed-sex group limited discussions about certain HIV prevention components, for example, VMMC. Given that the desired outcome of CAB involvement includes input into the design of risk-reduction strategies (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), in some

contexts, cultural norms may impede the full realisation of ethics recommendations, and deserves further detailed exploration.

Reservations about discussing sexual activity between different sexes also influenced the uptake of prevention interventions. For example, some male participants were uncomfortable disclosing STI symptoms to female clinicians, given gendered taboos about discussing sex (cf. Ndinda et al., 2011). While not explicitly reported in this study, it is plausible that socio-cultural taboos, may impact on risk-reduction counselling as well as other prevention interventions that rely on self-report, e.g., access to PEP.

In traditionally male circumcising communities, it was reported that customary practices of male circumcision limited uptake of VMMC at certain sites (cf. Mark et al., 2012), and may have also impacted on provider-promotion of this particular prevention intervention.

1.2 Gendered prevention practices

The provision of some prevention interventions, for example, counselling and female condoms, presented gendered challenges. Preconceived notions about women's sexuality and indoctrination of gendered norms which prescribe that women should be more conservative in their sexual behaviour than men, including that women should have fewer sexual partners (cf. Kelly & Bazzini, 2001; Kreager & Staff, 2009) impacted on the willingness of some female participants to disclose risky sexual activity during counselling sessions. A counsellor at one site noted this gendered dimension to social desirability bias in her observation of a female participant's reluctance to disclose that she had multiple sexual partners: “...it would have been better [easier to disclose] if she was a male” (Z4, site staff, site 2). Some work is being done to explore less biased methods for eliciting sexual risk behaviour electronically to eliminate the role of interpersonal inhibitions (e.g., Bowling, 2005; Dolezal et al., 2012).

Both trials sampled in this study enrolled male and female participants and in South Africa, women are at heightened risk for HIV infection (Abdool Karim, Siboko & Baxter, 2010; Leclerc-Madlala et al., 2009; Ramjee, 2013). While male condoms offer effective dual protection against unintended pregnancies and STIs, including HIV, male condom use may be difficult for women to negotiate (Langen, 2007). At the time this research was undertaken, the female condom was the only available female-initiated dual barrier method. Research has shown that when used correctly and consistently, female condoms are as effective as male

condoms (Vijayakumar et al., 2006). Other studies have demonstrated that availability of female condoms increased the number of protected sex acts (Barbosa, Kalckmann, Berquo & Stein, 2007) and a systematic review of 21 studies across various contexts demonstrated that increasing the availability and accessibility of female condoms improved condom use (Charania et al., 2011).

There was, however, a gender gap in condom provision in both trials and at all sites in this study. In the main, male condoms were consistently available, provided during counselling sessions, and at strategic places at the sites, e.g., restrooms. Further, the number of male condoms accessed was at the discretion of the participant. In contrast, female condoms were not always available, generally provided in counselling sessions and with a predetermined limitation on the number of condoms provided. This disparity in access may unwittingly validate perceptions that women have (or should have) fewer sexual partners than men (cf. Kelly & Bazzini, 2001; Kreager & Staff, 2009).

Shortages in supply of female condoms reported in this study mirror poor availability in the public sector. While South Africa's female condom distribution programme is one of the highest in the world, it is still woefully inadequate compared to male condom distribution (Beksinska, Smit & Mantell, 2012). In 2010/11, the South African DoH distributed just short of 100 male condoms for every female condom (DoH, 2011) and this variance may widen prospectively with a target of distributing 1 billion male condoms and 20 million female condoms by 2016 (SANAC, 2011). Further, in developing country contexts in general, there is a higher probability of an individual accessing ART than a reliable supply of female condoms (Oxfam, 2008). Challenges with availability and uptake of female condoms have also been reported in other empirical studies (Heise et al., 2008; Ngongo, Priddy, et al., 2012) and may relate to expense and availability (Padian et al., 2008; Surratt et al., 1998). Female condoms are approximately 18 times more expensive than male condoms (Beksinska et al., 2012). Some have even argued that erratic availability may have stifled demand (Parker, 2010). Respondents in this study also perceived the high cost as contributing to poor accessibility. However, given that VMMC was promoted and ensured, despite being significantly more expensive than female condoms, cost alone does not provide an adequate justification for sporadic access. Some have even contested that the provision of VMMC to male participants in trials that enrol both men and women may introduce a gender bias in terms of benefits accrued to participants (cf. McGrory et al., 2010). Since women in

developing countries, and particularly in Southern Africa, are at heightened risk for HIV infection (Quinn & Overbaugh, 2005; Ramjee, 2000), increasing access to female condoms should be ensured.

Gender and cultural norms and stereotypes may also influence the uptake of prevention interventions. Data from this study indicated that female condom uptake across sites was predominantly poor, citing reasons related to the product. Concerns that female condoms are noisy and too big have been reported elsewhere (Motsi, Banda & Mabvurira, 2012). Another explanation for poor uptake may relate to barriers including embarrassment or reticence to obtain condoms from sources that require in-person contact (UNFPA, 2002). Accepted notions of masculinity and femininity in many cultural settings dictate that women should be sexually innocent; this may create reluctance among females to request condoms from providers, carry them or suggest their use (Upadhyaya & Gumashta, 2012). Given reports in this study that for some female participants, disclosures of risky sexual behaviours is a challenge due to gender stereotypes, it is plausible that concerns about being perceived as promiscuous by counsellors, may impact on uptake.

Findings show that condom uptake is higher when not mediated by a provider (UNFPA, 2002; Wells & Alano, 2013) and since female condoms are generally obtained through provider contact and not through dispensers (Holt et al., 2013), this may negatively affect uptake. Therefore, changes in dispensing practices of female condoms appear to be indicated by this study.

Ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) mention concerns about gender and cultural dynamics primarily in terms of informed consent practices but recommend that counselling be gender and culture sensitive (MRC, 2003; UNAIDS/WHO, 2012) and that monitoring activities evaluate the extent to which this is achieved (UNAIDS/WHO, 2012). GPP guidelines (UNAIDS/AVAC, 2011) acknowledge that there may be socio-cultural taboos around certain trial procedures. However, except for counselling, guidelines do not anticipate that the provision of prevention services may present gendered complexities nor that cultural and gender dynamics may constrain community input into the design of prevention interventions.

Data from this study indicate that consistent with guideline recommendations to enhance socio-cultural competency (UNAIDS/AVAC, 2011), trial site staff are fairly knowledgeable about the socio-cultural context within which they operate, and how culture and gender norms may promote or constrain uptake of particular prevention interventions. However, the fact that cultural prescriptions may impede CAB inputs and that some prevention interventions may present gendered challenges was not always anticipated by trial implementers.

1.3 Power dynamics

Given that HIV prevention research is often funded by high-income countries and conducted in lower- and middle-income countries, the potential for power dynamics to impact on research has been widely acknowledged both in the literature (e.g., Emanuel et al., 2004; Essack, Koen, et al., 2010; Gahagan et al., 2008; Macklin, 2010; MacQueen, 2011) and ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). This is fairly predictable, given the differing positions, interests and mandates of various HVT stakeholders, including sponsors, investigators, host governments and communities. These concerns were borne out in this study, which revealed that real and perceived power dynamics were imbued across all phases of research. This data augments the guidelines and literature by detailing how power dynamics influenced the standard of prevention in practice.

One of the most common appraisals of power can be found in French and Raven's (1959) typology of five power bases. They contend that A's power over B is determined by: 1) A's ability to provide benefits to B and the extent to which B believes A controls these rewards (reward power); 2) A's ability to punish B if B does not comply with A's wishes (coercive power); 3) A's possession of special knowledge or expertise (expert power); 4) A's lawful authority to influence B (legitimate power); and 5) the extent to which A appeals to B or B identifies with A (referent power). This model is applied to the sections on power dynamics below.

1.3.1 Power dynamics at protocol development level

The protocol development committee was portrayed as the primary decision-making body in terms of the standard of prevention. In theory, this committee, with representatives of key stakeholders from sponsoring and host countries, is likely to be characterised by power

differentials (real or perceived). This was confirmed by data which revealed perceptions that power dynamics impact on standard of prevention decision-making.

The negotiating power of stakeholder representatives within the protocol committee was perceived as imbalanced in favour of sponsor representatives. GPP guidelines (UNAIDS/AVAC, 2011, p. 18) recognise the ubiquitous presence of power dynamics between funders and funding recipients with respect to a range of issues, such as decision-making processes, priority setting, control of resources, and equitable recognition of input. Frustrations at these pervasive inequalities in power were revealed in some interviews where the rhetorical device of 'othering' was observed in discussions about the sponsor. The sponsor was sometimes depicted as the other 'not on the same boat' (Z5, site staff, site 2) as other stakeholders with reference to protecting participants. 'Othering' entails identifying those deemed as different from oneself or the mainstream and can reinforce or reproduce positions of domination and subordination (Johnson et al., 2004, p. 253). While the group typically referred to as the other is often the subordinate and marginalised group (Johnson et al., 2004), in this research sponsors were perceived to straddle both groups, as explained more fully below.

Firstly, sponsors were argued to be the dominant group with regard to their command of the decision-making power (cf. UNAIDS/AVAC, 2011) and to hold the upper-hand in standard of prevention negotiations through the subjection of funding recipients to rigid funding policies. Anxiety, albeit from one respondent, that being too demanding may result in sponsor 'shopping' for more amenable trial sites (cf. Schüklenk, 2010; Upton, 2011) illuminates the perception of the sponsor as omnipotent 'there was a perceived threat that sites were compelled to restrict their budgetary requests to comply with sponsor policy or risk being deserted in a very competitive funding environment. Concerns that requiring sponsors to assume the responsibility of providing prevention services may make sites less attractive to some funders, were also raised at an introductory consultation for the present study (Essack et al., 2009). These sentiments also hinted at uneasiness that sponsors may 'prey' on less experienced and vulnerable sites, tipping the negotiations further in the sponsor's favour. This evokes concern about the potential for exploitation inherent when developed countries conduct research in developing country contexts (cf. Emanuel et al., 2004; Macklin, 2004). In this regard, it is argued that collaborative partnerships between stakeholders in the sponsor and host countries may minimise the possibility of exploitation (Emanuel et al., 2004).

However, some respondents in this study indicated their frustration with inflexible funding policies and questioned whether the protocol development process was truly collaborative.

Secondly, sponsors were also marginalised as ethically ambiguous in that they were perceived as protecting their own interests rather than being concerned about the welfare of participants (see Chapter 7). It is not surprising that a *‘othering’* discourse was evoked in interviews since research stakeholders involved in determining the prevention package had various competing interests (cf. UNAIDS/AVAC, 2011), which may reinforce power imbalances.

Despite concerns of power asymmetry between sponsors and researchers, this data also indicated that investigators represented on the protocol committee wielded considerable decision-making authority in standard of prevention determinations. For example, while sponsor policy dictated that funds could not be used for VMMC and STI treatment, investigators *“pushed very hard”* (Z9, network representative) to ensure that a comprehensive prevention package was ensured for trial participants. Therefore, rather than victims of a skewed power dynamic where sponsors control the resources and researchers compete for these resources (reward power), investigators are also powerful influencers of decisions and showed resolve in ensuring a *‘state-of-the-art’* prevention package for participants. This is in line with suppositions that PIs *‘are key decision-makers in the research hierarchy’* (Haire, 2013, p. 2).

However, there were key differences in the standard of prevention across trial protocols *‘in the phase I trial, a comprehensive prevention package was not written into the protocol; neither was such a package offered in some of the other trials referenced by respondents in this study. This may suggest that investigator influence worked in tandem with other factors to determine the standard of prevention, including the phase of the trial. Alternatively, this influence could be investigator-specific ‘reliant on the personal characteristics and convictions (referent power), as well as experience (expert power) and perceived power of the investigator. The latter, based on individual characteristics, present an arbitrary criterion, unlikely to be possessed by all investigators. Therefore, less experienced or less powerful investigators are unlikely to be as vociferous in their demands. In such circumstances, it is plausible that a lower standard of prevention could be settled upon during protocol development.*

In terms of community input into the protocol, one of the key challenges with authentically and meaningfully engaging communities in protocol development was the presence of an inherent power dynamic between sponsors/researchers and the lay community. Further, the current discourse on community partnership in research does not adequately recognise the entrenched power imbalances between communities and trialists (West Slevin et al., 2008). Many CAB and community members do not possess the basic tools necessary to engage, partner or negotiate constructively in debates on science, protocols (West Slevin et al., 2008) or the standard of prevention. Similarly, at a consultation on standards of prevention, participants raised concerns about whether the requirement for negotiation is realistic given the knowledge and power differentials that often characterize the relationships between a research enterprise and community advisory structures (McGrory et al., 2010, pp. 20-21). These power inequities create scepticism regarding whether communities can make meaningful inputs into standard of prevention decisions (cf. Macklin, 2010).

In recognition of this potential imbalance of power, CAB representatives on the protocol committee were reported to have received network-provided support, including capacity building on standards of prevention, in order to facilitate their meaningful engagement and participation in the protocol development process. This practice is in line with recommendations in normative frameworks (MRC, 2003; Tarantola et al., 2007; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) to develop the capacity of communities to make decisions. Community engagement should aim to minimise power differentials and create mechanisms for addressing deep-rooted power differentials (West Slevin et al., 2008).

In terms of within-stakeholder power differentials, it was reported that the manner in which CAB representatives were selected for protocol committees perpetuated perceptions of marginalisation among some CAB members at other sites. Similarly, investigators at some sites perceived a more limited role for themselves in making substantive inputs into the standard of prevention; rather, this role was advanced to the national PI or protocol chair. Challenges with ensuring meaningful community engagement reported in this study reflect pragmatic and logistical constraints, and the need for improved research literacy, rather than disagreement with ethical norms for community engagement.

Relationships of power inform the quality of community engagement (Upton, 2011). The ideals of community engagement embodied in ethics guidelines (MRC, 2003;

UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) reflect high expectations when compared to on the ground experiences (Upton, 2011). Therefore, while the protocol team ticks the boxes for collaborative decision-making, given the nominal representativity of key stakeholder groups, this data questions: 1) whether inherent power dynamics between and within stakeholder groups compromise the consultative and inclusive nature of such decisions and 2) given observed power differentials, whether negotiation of the standard of prevention is the most suitable mechanism for decision-making.

1.3.2 Power dynamics at protocol review level

Ethics guidelines recommend that community representatives participate in the review of the trial protocol (UNAIDS/WHO, 2012) and make inputs into the informed consent process (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Across sites, CAB representatives were involved in the review of relevant study materials, including ICFs and protocol summaries, and at some sites, CAB representatives were able to review the protocol in its entirety. Data from this study revealed the perception by some, that CAB review of study materials and/or protocols was a tokenistic exercise in community engagement. Simultaneous review of protocols by REC members and CABs was considered by some as disingenuous and limiting the power of CABs to make substantive inputs into protocols. This perception was challenged by the assertion that there have been instances where CAB input has resulted in changes to the protocol, even post-REC approval.

CAB members expressed frustration that they had limited authority and no legal power (≠legitimate power) to demand changes to protocols. The SA National Health Act (2003) makes the ethical review of research a statutory requirement, with RECs considered the primary protectors of human research participants (Dhai, 2005). The National Health Act (2003) recognises two roles for RECs, namely, 1) reviewing research and ensuring that it is relevant; and 2) granting approval for research when it meets ethical standards. Unlike this power bestowed to RECs by law (NHA, 2003), it has been contended that there are no legal requirements for community oversight of research in South Africa (Reddy et al., 2010).

While guidelines emphasise that the desired relationship between stakeholders is that of *equal* partners (UNAIDS/AVAC, 2011), perceptions of power imbalances are likely to strain the ability to operate as equals (cf. Cargo & Mercer, 2008). Inequalities in power can be accentuated in circumstances where there is an imbalance in literacy, education and economic

resources (UNAIDS/AVAC, 2011) or legal authority. In order to achieve meaningful participation, such structural power imbalances between stakeholders should be recognised and strategies implemented to overcome them (UNAIDS/WHO, 2012). Key strategies could include stakeholder outreach, engagement and education (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), including developing stakeholder knowledge and understanding of the research process and fostering research literacy (McGrory et al., 2010; UNAIDS/AVAC, 2011). Meaningful stakeholder engagement is essential for building research literacy. Reciprocally, improved research competency is likely to facilitate the active and meaningful engagement of stakeholders in the research process (UNAIDS/AVAC, 2011). In South Africa, findings regarding HIV-related knowledge have been mixed (van Loggerenberg et al., 2012), with relatively low knowledge of certain HIV risk-reduction measures reported in some studies (Shisana et al., 2009) and a recent regression in public knowledge of HIV and HIV prevention (Shisana et al., 2014). Therefore, to ensure effective decision-making, CABs need ethics and research literacy training so that they are able to critically evaluate study protocols and actively engage with the research.

Some commentators have suggested another mechanism to address concerns about unequal legitimate power and truly enable the CABs responsibility to protect participants and community members. It is argued that CABs must have real power and binding decision making authority, equal to that of a researcher or Research Ethics Committee (Reddy et al., 2010, p. 7). The argument that CABs have no legal authority is debatable however, since the National Health Act affords legal weight to national ethics guidelines, including MRC (2003). These guidelines (MRC, 2003) recommend community inputs into all phases of the research. The gap between guidelines and practices is however perpetuated by the absence of guidance for RECs on how to enforce principles of community engagement in research, including the implementation of GPP guidelines (UNAIDS/AVAC, 2011). Further, data from this study indicate that CAB knowledge of both substantive and implementation issues on the standard of prevention, was inadequate. Challenges in grappling with substantive issues identified in this study may reflect that in the past CABs were involved primarily in the procedural aspects of research, where rather than *determining* benefits, their role was to *communicate* risks and benefits to participants and the wider community (Cox, Rouff, Svendsen, Markowitz, & Abrams, 1998; Morin et al., 2008; Strauss et al., 2001). Further, Slack (2014) identified the concern that 'unreasonable' requests may be solicited during consultation processes with CABs. While attractive from a collaborative and participatory

perspective, before considering ratifying the legitimate power (French & Raven, 1959) of CABs, significant efforts must be made to enable CABs to make empowered and valid decisions.

In this study, CABs' perception of their power or powerlessness was also related to their specific roles. For some, changing the name of the CAB was perceived to fundamentally encroach on their role. The rhetorical power of changing the name from 'community advisory board' to 'community research support group' perpetuated perceptions that the advisory power of CABs was meaningless since "*the power of advising had been taken away*" (C1, site staff, site 1). This frustration suggests that CAB members place immense value in their 'advisory' role to sites and communities. Through their Masikhulisane training (Galloway, 2005), CABs reported that one of their key roles was advocating for trial participants. However, given ethics guidelines' (UNAIDS/WHO, 2012) emphasis on maintaining participants' confidentiality, at most sites CABs were denied direct access to participants. Where such relationships between CABs and participants were encouraged, CABs perceived access to participants as a 'powerful strategy' in fulfilling their role as advocates (Slack, 2014).

The need for improved capacity of CABs and RECs to critically review protocols in terms of the substantive issues was noted by respondents. A lack of capacity in CABs and RECs to review critical issues like the standard of prevention tips the balance of power in favour of science rather than the welfare of participants. Concerns that poor research literacy may impede the ability of some CABs to actively engage in research, including the review of study protocols have been raised elsewhere (Koen et al., 2013; West Slevin et al., 2008). However, lack of scientific understanding does not automatically preclude active community participation in such decisions. While poor scientific language and understanding may be an impediment, there are many examples of where communities have found innovative ways of communicating and explaining complex scientific concepts (Ndebele, Wassenaar, Munalula & Masire, 2012; Upton, 2011). For example, the concept of a vector is explained as analogous to a spoon used to get sugar from a bowl into a cup of tea (Upton, 2011). Such clear explanations dissolve divisions in terms of cultural understandings and educational levels, especially where deficits in science education continue to be problematic for most South Africans (Upton, 2011). UNAIDS/WHO (2012, p. 22) recommends 'capacity-building programmes in the science and ethics of biomedical HIV prevention research by relevant

scientific institutions and local and international organisations as well as early involvement of communities in the design and implementation of HIV prevention product development plans and protocols.

REC review of the standard of prevention in protocols and ICFs was limited to ascertaining the presence of such a package, rather than addressing the more substantive issues. Similarly to reports in this study, a previous survey of South African RECs also indicated that consideration of substantive ethical issues like standards of prevention and care are impeded by procedural and bureaucratic demands (Moodley & Myer, 2007). Findings of variable research ethics capacity on RECs and the need to build health research ethics capacity on these committees (expert power) is supported by previous research. Milford, et al. (2006, p. 5) found the majority (73%) of REC members who had previously reviewed HVT protocols agreed that there was a lack of general and sufficient ongoing training for members in health research ethics. In response to this need, there have been several initiatives to build health research capacity in Africa (Ndebele et al., 2014), including:

funding from the WHO-UNAIDS African AIDS Vaccine Programme (AAVP); the African Malaria Network Trust (AMANET); the National Institutes of Health (NIH) Fogarty International Center's South African Research Ethics Training Initiative (SARETI); the International Research Ethics Network for Southern Africa (IRENSA); the West African Bioethics Initiative (WAB); the Wellcome Trust; the European Union (EU); the Global Bioethics Forum; the World Health Organization (WHO), and the EU European Developing Countries Clinical Trials Partnership (EDCTP) which partially funds, for example, a high-level online capacity building programme known as TRREE (Ijsselmuiden, Marais, Wassenaar & Mokgatla-Moipolai, 2012, p. 3).

1.3.3 Power dynamics at protocol implementation level

The power to influence standard of prevention decisions was also observed at implementation. This study found that provider beliefs about a prevention intervention may temper if, how and when it is provided to participants. For example, respondents identified concerns about mechanical promotion of condoms, anxieties about promoting VMMC in certain cultural contexts, and concerns about the efficacy of PEP all of which point to the critical role of provider attitudes in uptake of services (Bharat & Mahendra, 2007; Hoffman, Mantell, Exner & Stein, 2004). In this way, providers have some influence over the prevention package offered to trial participants and/or participant uptake of prevention interventions. According to French and Raven's (1959) typology, this influence can be classified as expert power, since research staff may be perceived as possessing special knowledge or expertise. Further, power inequalities are inherent in patient-provider

relationships (UNAIDS/AVAC, 2011) and this may transcend to research. Authority usually resides with people in particular positions (õlegitimate powerö) or with special expertise (õexpert powerö) (Cheng, 2009). Deference to authority and/or expertise is still a feature of much South African culture given its history of colonisation. Previous research on stakeholders' perspectives on the ethics of HVTs in South Africa identified this concern: '... and coming from this disenfranchised type of history. . . most participants are still under that belief that the investigator knows it all' (Essack, Koen, et al., 2010, p. 14). The underlying belief in the omniscience of medical researchers (Newman et al., 2011), may hold significant power in framing participant choices. It has been observed that average people submit to the demands of authority with very little conscious deliberation and that even mere symbols of authority (e.g., titles, uniform, insignia, epaulettes) may be enough to elicit compliance (Cheng, 2009).

That the role for providers in determining standard of prevention options for participants may increase as the standard of prevention evolves, was identified by a PI at one site. As the menu of prevention tools expands, providers may increasingly be tasked with helping participants determine the best combination of services for their individual risk profiles. Enabling participant preferences in terms of which prevention options to take up is in line with the ethical principle of respect for autonomy. Respect for autonomy obligates researchers to recognise trial participants as individuals who have the right to make their own decisions, even when such decisions are based on values or worldviews that do not accord with those of the provider (Entwistle, Carter, Cribb & McCaffery, 2010). Respect for autonomy also entails that researchers create conditions necessary for participants to exert their autonomous choice. It would extend to ensuring access to prevention options and ensuring comprehensive counselling on all prevention options in enabling participants to make their own decisions about which prevention interventions, if any, are most appropriate for them. Therefore, adequately informed, skilled and motivated providers are central to participant uptake of services.

2. Defining the standard of prevention through consultation, consensus, and negotiation

Ethics guidelines do not prescribe a process for decision-making (Haire, 2013; Philpott, 2011) but different mechanisms for standard of prevention determinations are recommended,

including, agreement/consensus (UNAIDS/WHO, 2012), consultation (MRC, 2003; UNAIDS/WHO, 2012) and negotiation (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012).

These data indicated support, especially among CAB respondents, for consultation on the standard of prevention grounded in the ethical principle of respect for communities (cf. Weijer, 1999). However, this ethical recommendation was questioned by some respondents in this study as potentially opening up consultation to too many stakeholders. This concern may derive from the redefining of 'community' as all research stakeholders (cf. UNAIDS/AVAC, 2011), which has been argued as failing to 'clarify who exactly researchers should engage with, at what time-points, and to what ethical end' (Koen et al., 2013, p.147). Findings from a parallel quantitative study indicated that respondents did not overwhelmingly support the stakeholder consultation recommendation (Moorhouse et al., 2014).

In resonance with perceptions of respondents in this study, being over-inclusive in selecting stakeholders for consultation has been suggested to impede good stakeholder engagement (Koen et al., 2013; McGrory et al., 2010). Further, requiring all stakeholders to contribute to all levels of the research process without considering their expertise or their priorities is incompatible with the principle of respect for communities (Koen et al., 2013).

Commentators have argued that while communities should be involved in decisions that affect them, decisions which require high-level scientific or technical expertise may be exempt (Koen et al., 2013). Meaningful engagement, as opposed to tokenistic engagement, would require that relevant stakeholders be involved in decision-making 'about trial aspects for which they have expertise' (Koen et al., 2013, p. 147). Similarly McGrory et al. (2010) contend that while it may not be substantively or logistically feasible to consult all research stakeholders on all issues, it may be more appropriate and practically achievable to identify which specific stakeholders can best address different aspects of a trial (McGrory et al., 2010). The procedural recommendation requiring negotiation among research stakeholders that considers trial feasibility may not lend itself to inputs from those without requisite scientific and statistical expertise. Given that technical value judgements are warranted for feasibility determinations, this ethical recommendation has been criticised as favouring the research enterprise since feasibility determinations 'can only be made by the research elite' (Haire et al., 2013, p. 23).

Secondly, these data identified challenges with how best to operationalise the ethical requirement for stakeholder consultation. Respondents were particularly averse to large consultative meetings, such as those suggested by the good governance model (Tarantola et al., 2007). In practice, consultation formats varied and included formal and informal dialogue. The involvement of various stakeholder representatives in the development and review of protocols was also regarded as an adequate consultative device. Therefore, while the ethical requirement of stakeholder consultation on standards of prevention was supported, guidelines need more specification in terms of which particular stakeholders to consult on which aspects of the standard of prevention, what format such consultations should take (e.g., meetings, protocol reviews) as well as the frequency and time-points of consultations (cf. Koen et al., 2013; Moorhouse et al., 2014). Consideration should be given to refining the good governance model to reflect these concerns.

Findings from this study indicate that trial implementers and other key stakeholders questioned ethics guideline requirements that trials should not be conducted without the agreement of all research stakeholders on the standard of prevention (UNAIDS/WHO, 2012). This recommendation does not consider that consensus may be difficult to achieve and evaluate (Essack, Slack, et al., 2010). There is obvious value in consulting relevant research stakeholders on how best to operationalise standard of prevention decisions, although substantive ethical decisions are not best achieved by consensus (Stobie & Slack, 2010, p. 151). Some commentators have called for a procedural approach focussed on structured negotiating processes for making decisions on the evolving standard of prevention (Hankins et al., 2009) and it is anticipated that large consultative meetings will help clarify obligations to participants (Tarantola et al., 2007). Still, given the lack of consensus on what constitutes appropriate standards of prevention at a substantive level, this approach only reassigns the difficult struggle with norms and standards to consultative meetings (Stobie & Slack, 2010, p. 151). Decision-making that is procedurally fair may not necessarily result in the morally right outcome (Ashcroft, 2008). Therefore, soliciting the perspectives of affected parties may be morally relevant but not morally definitive (Essack, Slack, et al., 2010; Grady et al., 2008; Slack & Stobie, 2010). Unless consultations are informed by substantive and normative principles and guided by formal structures for consensus decision-making, conflict and contention are likely; such consultations run the risk of limiting the input of less powerful, less vocal, and less intractable group members (Johnson-Masotti, Pinkerton, Holtgrave, Valdiserri & Willingham, 2000; Philpott et al., 2011).

Negotiation is another mechanism for decision-making (Cheng, 2009) and is a process of two (or more) parties combining their *conflicting* points of view into a single decision (Zartman, 1977, p. 622, emphasis added). Since power pervades all facets of negotiation (Cheng, 2009), it is unclear whether negotiation best serves the process of decision-making on the standard of prevention as the very idea of negotiation intuitively conjures images of power contests and tough bargaining (Cheng, 2009, Power section, para. 1). By definition then, negotiation is most likely to result in a compromise position rather than the substantive standard established in ethics guidelines. Asymmetries in power are likely to influence standard of prevention negotiations and determine the final outcome (Cheng, 2009). One of the criticisms of proceduralism in ethics is that processes of consensus and negotiation are favoured over establishing substantive norms (London & Zollman, 2010) and such processes may not best serve values of fairness (Schüklenk, 2010).

This was not just a hypothetical concern of some respondents, but has been evinced by this data which showed the pervasive influence of power during protocol development, review and implementation, as well as research showing that more powerful countries (e.g., the US) dominate exchanges with less powerful counterparts (Cheng, 2009). Previous research has also demonstrated that strict sponsor policies have influenced care and prevention services offered to participants (Heise et al., 2008; Philpott et al., 2010), including regarding protocol omissions on the care to be provided to participants (Slack, 2014).

Current ethical guidance in HIV prevention trials places disproportionate emphasis on negotiation, which given the substantial inequities between the negotiating parties is likely to result in outcomes that suit the interests of research enterprise over the interests of the research participant (Haire, 2013, p. 266). To date, most CABs at sites have not been tasked with the responsibility of negotiating evolving standards of prevention in trials (McGrory et al., 2010). This study found that practices for protocol development and review reflect efforts to engage community representatives to make inputs into the design of standards of prevention (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). However, like with HIV care and treatment (Slack, 2014), the recommendation for negotiation on standards of prevention was not realised in practice. It has been argued elsewhere (Haire et al., 2013) that structural inequalities between research and community representatives and between high- and low/middle-income countries constrain the ability to negotiate the standard of prevention. As evidenced by inequalities in power, research literacy and scientific expertise,

realising the ideals of negotiation will require significant improvements in the capacity of stakeholders to engage at this level (West Slevin et al., 2008), including a shared understanding of the scientific, ethical and political implications of such decisions (McGrory et al., 2010). These data support calls for the development, piloting and evaluation of frameworks to operationalise ethical requirements for consultation, consensus and negotiation (McGrory et al., 2010; Philpott et al., 2011).

In an assessment of GPP guidelines at research centres in eastern and southern Africa, respondents placed lower relevance at baseline on stakeholder engagement in protocol development and standards of prevention (Ngongo, Hannah, et al., 2012). A quantitative assessment of key stakeholders' perspectives on ethical guidelines also found that respondents did not overwhelmingly support the recommendation for stakeholder consultation for adding new tools to the prevention package (Moorhouse et al., 2014). Low scores were also awarded on dimensions of perceived protection for the recommendations of stakeholder consultation and negotiation; and overall the most poorly ranked recommendation was that stakeholders should negotiate adding new methods to the risk-reduction package (Moorhouse et al., 2014). This suggests that these recommendations are perceived as challenging for respondents and difficult to implement and understand.

3. Ensuring access to HIV prevention interventions: Sourcing funding and establishing partnerships

Ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) require that trial participants are ensured access to HIV risk-reduction interventions. Ensuring access to prevention interventions through a combination of on-site provision and referral has been reported in other empirical studies (Haire, 2013; Heise et al., 2008; MacQueen et al., 2008; Ngongo, Priddy, et al., 2012). This study found that South African HVT implementers favour the more onerous direct provision of prevention interventions over referral. The reasons for this preference included better monitoring of uptake, efficiency in service delivery, and improved participant retention. However, the ability to offer all prevention interventions on-site was inhibited by funding constraints.

3.1 Funding standard of prevention interventions in HVTs

Guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) obligate sponsors and researchers to ensure access (directly or via referrals) to prevention interventions, but

exactly who should assume the cost burden has been subject to debate. There has been some agreement that ensuring access to prevention interventions is a shared responsibility among sponsors, researchers and host governments (Macklin, 2008; Tarantola et al., 2007; UNAIDS/WHO, 2012) and that novel partnerships for ensuring access to prevention interventions should be developed and explored (Tarantola et al., 2007).

HIV prevention trials are expensive to conduct (MacQueen, 2011). For example, HVTN 505 was estimated to cost between US\$75-80 million (RTWG, 2013), a substantial amount in a finite and potentially dwindling pool of resources. Availability of research funding may become increasingly difficult given imminent budget cuts due to potential sequestration of funds from those federal agencies supporting HIV vaccine research (RTWG, 2013). Financing and resources for HIV prevention trials are obtained from several donors, each with their own interests, missions, mandates and policies – all of which impact on both the design and conduct of trials (Philpott et al., 2010). The US remains the largest investor in HIV prevention research and development, with US government agencies accounting for 74% of the total HIV vaccine research and development funding – 66% of which was contributed by the NIH (RTWG, 2013). In 2012, the NIH funded more than two-thirds of the ongoing HVTs (RTWG, 2013).

Notwithstanding this laudable investment in HIV vaccine research, one of the challenges of conducting research in developing country contexts is that the research process and funding are controlled by the sponsor (usually from a developed country context) and these funds come with specific instructions on how the money should be used to the satisfaction of the donor (Gwandure & Mayekiso, 2012, p. 174). Complexities regarding funding appeared to permeate both the design and implementation of the prevention package, and had implications for current and evolving standards of prevention. The standard of prevention was influenced by funding in two primary ways: it was constrained in terms of sponsor policy on what constituted allowable costs in research and it depended on whether research networks and investigators acquired funding from alternative sources or partnered with service providers to ensure access.

Donor funding comes with strict terms and conditions (Senanayake & Hamm, 2004). For example, donors like the NIH have policies that prevent the use of donor funds for non-research related care (Heise et al., 2008; Philpott et al., 2010). In its grants policy statement

(2013), the NIH specifies that as a federal grantor agency, it is responsible to Congress and US taxpayers in executing its mission to facilitate research both cost-effectively and in compliance with applicable rules and regulations. Policymakers have interpreted the NIH's authorising legislation as barring the use of taxpayer dollars for the procurement of drugs or the provision of non-research related care (Philpott et al., 2010). Similarly, respondents in this study, including research network representatives and investigators, interpreted the sponsor policy as prohibiting the purchase of drugs for the treatment of STIs or for PEP, and the provision of VMMC. Concerns that funding restrictions may limit which prevention methods can be ensured through donor funds are anticipated by some guidelines (UNAIDS/AVAC, 2011). On the contrary, Haire (2013) argues that NIH policy does not restrict the provision of standard of prevention interventions, including STI-based HIV prevention services and condoms. These diverse interpretations affirm the need for sponsors to develop clear and understandable funding policies (Heise et al., 2008).

Respondents perceived sponsor policy as rigid, non-negotiable and a 'cop-out' by definition, a 'cop-out' entails avoiding doing something that one ought to do (Oxford Dictionaries, 2014) or failing to fulfil a commitment or responsibility (American Heritage Dictionary of the English Language, 2009). Respondents argued that sponsor policy and related funding restrictions made it possible for sponsors to renege on their ethical obligations to ensure access to HIV risk-reduction interventions for trial participants. In this way, sponsors were sometimes portrayed as flouting their ethical responsibilities to advance their own interests to carry out research efficiently and effectively, given their primary mission to conduct research as opposed to providing health benefits to research participants (cf. Macklin, 2004). Further, because sponsors controlled the funding, some respondents considered them to command supreme decision-making authority to the extent that standard of prevention determinations were perceived as 'obscured at the top, with ill-defined or inconsistent donor policies that restrict what is considered 'possible' (Heise et al., 2008, p. 75).

The potential for sponsors' policies to impact on standards of care and prevention have been reported in other empirical studies. Findings from the HPTN's partnering for care study indicated that researchers 'were keenly aware that the funding they received for research had strict rules governing how it could be used' (MacQueen et al., 2008, p. 11). The standard of care mapping study conducted by the GCM found that donor policies that restricted how

research funds may be used, limited the level of care provided to participants (Heise et al., 2008; Philpott et al., 2010). In contrast, Haire (2013) found that most investigators reported that sponsor policies positively influenced the provision of prevention services. Still, some respondents did indicate frustration with funding policies, for example, “[w]e informed community leaders of what we could offer, but there was not much we could negotiate! It is often assumed that the researchers make the decisions as to what to offer, but in many cases, our hands are tied” (Haire, 2013, p. 102). The metaphor “our hands are tied” echoes the frustration of respondents in the present study, that there was little that could be done to remedy limitations imposed by sponsor funding policy. Similarly, sponsors may argue that their “hands are tied” by the authorising legal framework and accompanying rules and regulations. Constraints imposed on funding by US federal regulations have also been critiqued because they preclude compensation for research-related injury (Cleaton-Jones & Wassenaar, 2010; Mamotte et al., 2013). However, the recent U.S. Presidential Commission for the Study of Bioethics Report (2011) recommended changes to policy and that participants are morally entitled to compensation for research-related injury. Despite the constraints imposed by sponsor funding policy, trial sites did actually provide access to a range of HIV prevention interventions.

3.2 Partnering for prevention

Guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) require that counselling should be provided to participants and that access to prevention interventions should be ensured. This distinction in obligations (actually provide versus ensure access) may explain why counselling was the only prevention intervention described in the phase I protocol and in the ICFs for both trials. While donor funding supported the provision of risk-reduction counselling (by paying salaries of counsellors), other components of the prevention package were ensured through various strategies. More specifically, male and female condoms were procured from the DoH, at no cost to sites. For STI treatment, sites had to engage the DoH to dispense STI treatment on-site, or themselves raise funds; alternatively they made referrals to the public healthcare sector. Further, the research network raised funds to pay for VMMC in the phase IIB trial only. Various strategies were used to ensure on-site access to PEP, including, through a “site kitty” (Slack, 2014), and/or procured from the DoH or other sources like PEPFAR, or provided through the study budget. Alternatively, participants were referred to the public healthcare sector where PEP could be accessed in cases of sexual assault only.

Restrictions on sponsor funds for care provision not necessary for scientific validity or participant safety (Philpott et al., 2010) have led researchers to partner creatively with other stakeholders in ensuring access to key prevention services. Site practices for ensuring access to prevention interventions indicated that the burden of providing prevention interventions is shared among sponsors, researchers, government service providers, and in some instances private donors, as recommended in guidelines (cf. UNAIDS/WHO, 2012) and by key commentators (Macklin, 2008; Tarantola et al., 2007). Further, sourcing alternative funds and partnering with service providers to ensure access to prevention interventions resonates squarely with guideline recommendations (UNAIDS/AVAC, 2011).

Given this complex funding environment, site practices indicated the critical role of collaborative partnerships in ensuring access to standards of prevention. The South African DoH (and by inference the government) emerged as a key partner in ensuring access to prevention services, serving as both a procurement source and a service provider. A key characteristic of the success of these partnerships was that they were mutually beneficial ó in exchange for free condoms and STI treatment, sites provided the DoH with statistics that contributed towards provincial and national performance targets. These data have indicated that host country governments through provincial and local healthcare systems have taken responsibility in delivering prevention interventions to participants. Such partnerships ensure that national authorities are fully engaged in the decision-making process and that interventions are sustainable post-trial (Tarantola et al., 2007). Still, engaging this partner was associated with some tensions, for example, limited accessibility of female condoms or constraints on STI treatment at public sector facilities, as predicted by some authors (Chatterjee et al., 2006). Further, the range of prevention interventions that could be ensured through this partnership were confined to their national availability (cf. UNAIDS/AVAC, 2011). At the time that the two trials were initiated, the standard of prevention in South Africa included HCT, male and female condoms, and syndromic management of STIs. VMMC was not yet rolled out as an HIV prevention intervention (de Bruyn, 2009) and PEP was (and still is) limited to occupational injuries and for rape survivors (SANAC, 2011) who have reported the sexual assault to the police.

Reported practices related to adding VMMC to the prevention package indicated that funding complexities were also relevant as the standard of prevention evolved. Since sponsor funding was perceived to prohibit the provision of VMMC in HVTs, funding was sourced by the

research network from the product developer for the phase IIB trial. Network representatives confirmed that as the standard of prevention evolves, it remains unlikely that prevention interventions like PrEP or microbicides will be supported via donor funds, and that it will become increasingly important to develop strategic partnerships in order to source alternate funds (cf. Tarantola et al., 2007). The present data reaffirm recommendations for donors to develop and implement funding policies that are clear and understandable, that are objectively and scientifically based, and that enable and encourage researchers to ratchet up the local standards of care in a manner that is sustainable even after a study ends (Heise et al., 2008, p. 72). Similarly, the International Research Panel of the Presidential Commission for the Study of Bioethical Issues (2011) recommended that existing regulations need to be reviewed and refined given that clear, sound and harmonised rules promote efficiency and quality.

Commentators, including some respondents in this study, have suggested that cost is an inadequate justification for not ensuring access to new scientifically validated or approved prevention interventions (e.g., Cowan & Macklin, 2014; Haire, 2013). However, data from this study indicated that in practice the standard of prevention ensured in HVTs depended on a host of factors including the study budget, donor policies, site availability of funds and the standard of prevention available in the host country. Therefore, cost is a relevant additional criterion to consider when making decisions to add a new prevention intervention to the prevention package (Jay et al., n.d.; McGrory et al., 2010; Tarantola et al., 2007).

Researchers may increasingly call on their partnerships with government in ensuring access to prevention interventions given that the available prevention interventions offered in the public sector may evolve in the future. The current NSP (SANAC, 2011) specifically calls for the consideration of new modalities for HIV prevention, including PrEP, microbicides and PEP for all risky sexual exposures; however, it notes that further work is still required on the feasibility of implementing these strategies. The NSP states that policy decisions on the introduction of PrEP and microbicides will depend on scientific evidence of efficacy, guidance from international bodies and the registration of such interventions with the MCC for use (SANAC, 2011). Such policy-level deliberations consider scientific evidence from clinical trials, including factors such as cost-effectiveness, feasibility, scalability, and competing healthcare needs (Dawson, 2012).

In addition to the cost of ensuring access to interventions, as the standard of prevention evolves the need to increase the number of trial participants to meet study endpoints, will also amplify costs ó all in a context of increasing research costs and diminishing budgets (Haire et al., 2012; RTWG, 2013). Together, these data indicate that diversifying funding sources, solidifying existing partnerships, and establishing new collaborations will be essential as the standard of prevention evolves and as South Africa seeks to expand trial site capacity to conduct large-scale efficacy trials towards the development of a licenced vaccine (Esparza, 2013).

4. Double standards of prevention

Raging debates about ethical double standards in research emerged in 1997 over the PMTCT trials conducted in developing country contexts and evaluating experimental regimens against placebo-controls rather than the established effective intervention (ACTG076) that had become standard practice in the US (Angell, 1997; Lurie & Wolf 1997). Some contested that the use of placebo in these trials constituted a double standard in research ethics between developed and developing countries (Angell, 1997; Lurie & Wolf, 1997). However, others argued that the ACTG076 regimen was not affordable or feasible in developing country contexts; rather, the research question was whether the experimental intervention was better than the status quo of nothing (Varmus & Satcher, 1997). This controversy positioned those who argued for a universal standard against those who argued for a context-specific interpretation. These trials, deemed unethical by critics, demonstrated that a single dose of nevirapine could effectively and sustainably reduce mother-to-child transmission of HIV, which had a profound impact on perinatal HIV treatment in developing countries, including South Africa (Coetzee et al., 2005; Colvin et al., 2007).

The choice between ‘best-known’ and ‘best available’ standards of care as the comparator arm of clinical trials remains a fundamental ethical dilemma for trials in resource-constrained contexts (Dawson et al., 2014). Data from the present study revealed that concerns about so-called double standards exist beyond the pre-occupation with ensuring parity between developed and developing countries. The theme of double standards captures this concern as well as variability in decision-making about current versus evolving standards of prevention and the potential for differences in standards of prevention both within and across trial sites in the same country.

4.1 Local versus international ‘state-of-the-art’

Contentions abound about whether the standard of prevention should be benchmarked against the best available in the world, the local standard of prevention, or somewhere in between. Some guidelines (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) have argued that a ‘state-of-the-art’ prevention package be ensured for participants. However, disagreement remains, even at the level of ethics guidelines (HPTN, 2009; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), about whether standard of prevention packages should be benchmarked on international or national standards. While the recommendation that state-of-the-art prevention interventions be provided to participants has generally been interpreted as benchmarked on universal best practice (Haire, 2013; Macklin, 2009b), guidelines also assert that clinical trials should be integrated with national prevention plans (UNAIDS/WHO, 2012) and that negotiations and discussions consider current standards of prevention and services available nationally and locally (UNAIDS/AVAC, 2011). These ambiguities open guidelines to multiple interpretations, which may create real differences in the standard of prevention for trial participants.

Earlier versions of UNAIDS guidelines referred to ‘proven’ and ‘validated’ methods; these terms were contentious, and their replacement with ‘state-of-the-art’ was assumed to strengthen the guidance point (Macklin, 2012). However, data from this study indicated that rather than being unambiguous, the state-of-the-art standard is ‘in the eye of the beholder’ that is, a matter of personal opinion. The term ‘state-of-the-art’ was argued to be vague and enabling multiple interpretations as evinced by the lack of consensus even among respondents on what was considered state-of-the-art. Concerns that ‘state-of-the-art’ is too vague have been reported elsewhere (Haire, 2013; McGrory et al., 2010; Philpott et al., 2011). The diversity of opinion on what constitutes ‘state-of-the-art’ contradicts the supposition that there is increasing consensus that a state-of-the-art prevention package should be provided to participants (Macklin, 2008). While it was acknowledged that vagueness permits flexibility given the evolving nature of standards of prevention as well as changing circumstances (cf. Macklin, 2012), vagueness may also enable the perpetuation of double standards. A parallel quantitative study (Moorhouse et al., 2014) found low scores on dimensions of implementability and understanding of prevention recommendations which may reflect that respondents struggle to interpret and operationalise key but broad concepts such as state-of-the-art.

Respondents in this study, especially REC representatives, strongly endorsed that standards of prevention be benchmarked against national rather than international policy. This perspective closely resembles the position of HPTN (2009) guidelines which advocate for a prevention package that can be feasibly implemented into local health systems. Similar perspectives were articulated in terms of ancillary care (Slack, 2014). Some of the arguments in favour of this position included minimising concerns about undue inducement, reducing disparities between trial participants and their communities, and ensuring sustainability of interventions post-trial. This reasoning closely resembles arguments in HPTN guidelines (2009) critiquing the 'state-of-the-art' standard. HPTN guidelines (2009) were founded on social justice principles, which entail avoiding exploitation, treating people equally and making efforts to minimise health disparities. The challenge for researchers conducting research in developing contexts is 'to improve health without taking unfair advantage of, or increasing, existing social inequalities' (HPTN, 2009, p. 10). Social justice demands that the standard of prevention not be radically superior to the current local standard of prevention as this would create inequities between trial participants and host communities (HPTN, 2009). While South African ethics guidelines (MRC, 2003) emphasise social justice among ethical principles, it also states that participants should receive services that they would not otherwise obtain.

Universalists argue that the researcher's primary obligation is to protect participants and that this would require importing standards of care and prevention from the developed world (Haire, 2013). Advocates of a universal standard contend that failure to provide state-of-the-art interventions is unjust and would constitute ethical double standards (Heise & Wood, 2005). Adopting the best international standard would also reduce the likelihood of inconsistencies among different sites in multicountry trials that may occur if standards of prevention are negotiated locally and based on local realities (Heise & Wood, 2005). However, the ideal of a universal fixed standard is not without challenges. Context is an important consideration because it impacts on determinations of feasibility and appropriateness of the intervention (Heise & Wood, 2005), as well as whether standards in guidelines can be applied in the actual research setting that presents unique political, social, economic, cultural and regulatory constraints and challenges (HPTN, 2009). For example, in practice, funding complexities and multiple other factors, constrain the implementation of the best available standard for all HVTs. Further, the 'state-of-the-art' is ever evolving (cf. Heise & Wood, 2005).

Relativists, in contrast, contend that community interests are best served by taking into account local realities; as such, the background standard of prevention should reflect the local baseline currently available in the community, even if that is nothing (Haire, 2013).

Respondents in the present study adopted a middle-ground position, maintaining that ‘perfect’ should not be the enemy of good. It was argued that the standard of prevention implemented in developed country contexts should not be imposed on developing contexts, where it is unlikely to be feasible. At a minimum, the standard of prevention in HVTs should be benchmarked on national standards, provided that this baseline is not wholly inadequate (cf. Heise & Woods, 2005). The present author supports the perspective that the standard of prevention be benchmarked against national rather than international standards, with the addendum that where scientifically validated prevention interventions are not nationally approved, sponsors, trial implementers, community representatives and research ethics committees should advocate for their approval. This is especially important given the potential for protracted approval in some contexts. The present researcher also endorses the provision of a higher standard of prevention than that locally available when it is feasible to do so, but contends that this would be morally praiseworthy rather than obligatory. In other words, researchers should make efforts to improve the standard of prevention but ensure that research remains relevant to the health context in which it is conducted (cf. Dawson et al., 2014). This position most closely concurs with Shapiro and Benatar’s view that the standard of care:

should be based on principles that promote fairer distribution of burdens and benefits, both short and long term for participants and communities. First, research should be undertaken in the best interests of trial participants by involving them in decisions around research design and implementation. Second, the dignity of participants should be respected, wherever they are in the world. Third, consideration should be given to the broader community benefit that could be achieved by raising the standard of healthcare through partnerships created by the research endeavour. That the ideal of first world healthcare cannot be achieved immediately in developing countries should not be a deterrent to efforts to raise existing levels of care. By setting high ideals and working towards them, the standard of care could be progressively ratcheted upwards (Shapiro & Benatar 2005, p. 44).

The ambiguity regarding whether the standard should be ‘best-known’ or ‘best available’ was evinced in practice with the addition of VMMC. In some trials, participants were offered VMMC based on evidence of efficacy while others waited for national guidelines on VMMC before implementation (Haire & Jordens, 2013).

4.2 Within-country differences in standards of prevention

This study found differences in the prevention interventions offered to participants enrolled on different protocols at the same site and across different sites. In terms of VMMC, securing funding for one trial (phase IIB) but not others created within-site differences between participants enrolled on different protocols. Given that participants can only be referred to the public healthcare system in cases of sexual assault (cf. DoH, 2008), ensuring funding for PEP for all risky sexual exposures for selected trials was a cause of frustration, particularly for newer sites that did not enjoy the benefits of a *õsite-kittyö* (Slack, 2014) to self-fund PEP. Therefore, where trials and sites use different approaches for prevention interventions (e.g., VMMC and PEP), this may create differences between participants enrolled in different protocols at the same site or between participants at different sites. These complexities may raise concerns about fairness if participants within the same country receive different benefits but endure the same level of risk.

Findings of variability in standards of prevention are not new. Empirical data have shown that the standard of prevention implemented in trials is variable (Heise et al., 2008; Ngongo, Priddy, et al., 2012) and anything but standard (McGrory et al., 2010). For example, Ngongo, Priddy, et al. (2012) found that prevention interventions such as female condoms, VMMC and PEP were not provided consistently across ten IAVI research centres. However, data from the present study identify that differences stemmed from a range of factors including whether alternate funds were secured, whether the site was able to self-fund services or whether they referred participants to the public healthcare system.

Ethics guidelines assert that protocols may vary in *õmodes of deliveryö* for prevention interventions (UNAIDS/WHO, 2012, p. 45), that negotiations should occur on a trial-by-trial basis (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) and that when funding restrictions limit which interventions can be provided, researchers should find alternative funding or establish partnerships to ensure access (UNAIDS/AVAC, 2011). This suggests that guidelines allow for some flexibility of approach to the implementation of standards of prevention. Some respondents valued the ability to make decisions on a site-by-site basis, although the unintended consequence of such decision-making may be inequitable outcomes for trial participants. Some commentators have endeavoured to develop a *õstandard approachö* to prevention services (Ngongo, Priddy, et al., 2012, p. 1278) while others have argued that standardised approaches may be constraining if mandated (Slack, 2014).

Current ethics guidelines provide little direction on within-country differences on standards of prevention. However, an earlier version of GPP guidelines (UNAIDS/AVAC, 2007, p. 29) recommended that trial sponsors should ensure that core elements of the prevention package are consistent across trials and networks. This resonates with the views of some respondents in this study as well as some Ugandan consultation participants who argued for developing a core, evidence-based prevention package that is feasible to deliver (McGrory et al., 2010, p. 20). In practice, this would entail mandating a standard of prevention package but allowing flexibility in the operationalisation thereof (e.g., on-site provision versus referral). This would minimise within and between site differences and ensure reasonably commensurate outcomes for participants (cf. Slack, 2014). However, at present no clear, specific international or national guidelines for the type of prevention package that must be provided in HIV prevention trials exist (McGrory et al., 2010, p. 20).

4.3 Ambiguities regarding regulatory approval

The recommendation that the prevention modality should be approved by the regulator in the host country before it is added to the prevention package (UNAIDS/AVAC, 2011) was espoused by respondents in this study. However, the companion guidelines (UNAIDS/WHO, 2012) do not specify whether approval of the national regulatory authority is required, or whether any regulatory or normative body approval would be sufficient (Haire, 2013). This opens guidelines to multiple interpretations, as aptly demonstrated by the range of perspectives on regulatory approval. On the one hand, it has been strongly argued that once a prevention intervention is approved by a regulatory authority in *any* country, it would need to be added into various other prevention studies as part of the 'standard prevention package' (Haire et al., 2012, p. 27). On the other hand, it is noted that the framing of the guidance point on the standard of prevention arguably provides a source of moral authority for delaying the introduction of a 'state-of-the-art' intervention until such time as it is listed in national guidelines (Haire, 2013, pp. 168-169). In view of the inconsistencies in guidelines and the potential for multiple interpretations, respondents in this study appeared to favour the stricter interpretation of guidelines by endorsing national regulatory approval. There is little consensus on this issue (Philpott et al., 2011). For example, in developing key criteria to guide standard of prevention decision-making, meeting participants at the Ugandan consultation agreed that once a new method has been recommended for use by relevant *international or national agencies*, it should be provided in trials; departures from this recommendation should be ethically and scientifically justified in the study protocol (Philpott

et al., 2011, emphasis added). Still, a number of participants emphasised that they expect new tools to be *nationally approved* and available before they are added to the prevention package (Philpott et al., 2011, emphasis added). Furthermore, it was noted that considerations of feasibility in terms of local availability and accessibility, manufacturing and importation restrictions are also relevant (Philpott et al., 2011). However, the endorsement of national regulatory approval has been criticised as unnecessarily and unethically delaying the introduction of new and effective HIV prevention interventions (Haire et al., 2012). In terms of the evolving standard of prevention, these dichotomous interpretations have bearing on the inclusion of PrEP in the standard of prevention in developing country contexts. PrEP is now considered scientifically validated and, barring exceptional circumstances, should be included in the standard of prevention of future HIV prevention trials (Cowan & Macklin, 2014; Haire, 2014). PrEP could also be argued to meet the clinical validation threshold specified in the three-step framework (Jay et al., n.d.). While PrEP has been approved by the US FDA (FDA, 2012), to date it has not been approved in any of the eight countries in which these trials were conducted, including South Africa (Bekker et al., 2012; Haire, 2013; Hankins & Dybul, 2013). Therefore, based on the endorsement of national regulatory approval by most respondents in this study, it is likely that they would argue that PrEP cannot be mandated as standard of prevention in South African HVTs, although they are likely to endorse that participants are educated about the benefits of PrEP and where it can be accessed.

The three-step framework however, argues that clinical validation is not contingent on regulatory approval and that in resource-constrained contexts, if the prevention intervention is considered an appropriate, realistic practice but has not been instituted in the local healthcare system due only to cost, the validation threshold is satisfied (Jay et al., n.d.). The exception relates to those prevention interventions that would severely constrain local healthcare system capacity, and are perceived as unsustainable and an inappropriate use of clinical resources. Such interventions are not considered clinically validated (Jay et al., n.d.).

Failure to include PrEP in the standard of prevention however, may pose complexities in multicountry trials both in terms of the interpretability of findings and ethical double standards between resourced and resource-constrained contexts (Haire et al., 2013; Haire, 2014). Further, given that some South African practitioners are already prescribing PrEP in the private sector (Rebe & McIntyre, 2014), HVT stakeholders would need to consider

seriously the impact on scientific outcomes if some participants opted to access PrEP privately. The HVTN 505 study conducted a survey among participants and found only a small percentage indicating intent to use PrEP, which appeared greatest if PrEP was provided in the trial or covered through medical insurance (Fuchs et al., 2013). After consultation with community stakeholders, the HVTN 505 team decided to offer education about PrEP to participants, include active behavioural and biologic monitoring of PrEP use, and collaborate with trial sites to ensure referrals to community providers. One suggestion has been that future trials include PrEP as an active comparator, which may help relieve the tension between finding new effective products while protecting trial participants (Haire, 2014). Finally, denying trial participants access to a prevention intervention simply because it has not been registered in the country where they live, has been argued to be ethically problematic (Cowan & Macklin, 2014). Despite the criteria endorsed by respondents in the present study, if mechanisms to ensure access to PrEP in HVTs are established (despite complex funding constraints), it is possible that RECs may indeed approve such prevention packages as occurred with VMMC and PEP.

These divergent perspectives raise important questions about the role of national regulatory authorities, and who should be the vanguard of decision-making for standards of prevention? Is it researchers, RECs and regulatory authorities in sponsor countries? If community participation principles are meaningfully implemented, would it not be their counterparts in host countries? It seems unlikely that researchers in the US would add a tool to the prevention package if it was approved by the South African MCC or a regulatory authority in another developing country, but not by the FDA? Of course, delays in regulatory approval will unduly prolong the provision of effective services to those who need it most (cf. Haire, 2013). But is the solution to flout national authorities all together or directly address such concerns with the regulatory authority, with an emphasis on expediency? Since PrEP can be considered scientifically validated and has been approved by the US FDA (Cowan & Macklin, 2014; Haire, 2013), it is seductively easy to conclude that PrEP should be added to standard of prevention immediately (Haire, 2013, p. 175). If this approach is mandated, the role of national regulatory authorities, important stakeholders in HVTs, and who have a valid role in determining which prevention interventions are prioritised in their countries, would be undercut (Haire, 2013). National regulators constitute a significant public good, whose primary objective is to protect the public from harm (Chilengi, 2009). Nevertheless, it is possible that PrEP products (e.g., Truvada) currently licenced for treatment may not need to

be approved by regulators for off-label use as prevention ó nevirapine, for example, is routinely provided in PMTCT programmes, although it has not been approved by regulatory authorities for this purpose (Kim et al., 2010). Such interventions are funded because of õbroad support and guidance from national and global normative bodies, such as WHOö (Kim et al., 2010, p. 4).

4.4 Perspectives versus practices

The availability of prevention interventions in the public healthcare sector was endorsed by several respondents as another criterion for consideration when determining the prevention package for HVTs. Such a locally customised package would circumvent the challenges identified with access to a state-of-the-art package (cf. HPTN, 2009) and guarantee sustainability of interventions post-trial. However, this is a lower requirement than was accepted and advocated for HIV treatment. South African guidelines (MRC, 2003, p. 33) described that õsome consensus existed that trial participants should receive better treatment and care than would be available to them in the current public healthcare system in South Africa.ö This may suggest ñdouble standardsñ in perspectives on standards of prevention and HIV treatment.

Despite the strong advocacy for a national benchmark and public sector availability by REC respondents in this study, actual practices reflect differences between perspectives and practices. For the phase IIB trial, RECs across South Africa approved the inclusion of VMMC and PEP for all risky sexual exposures as standard of prevention despite these services not routinely being offered in the public sector, and in advance of national guidelines on VMMC. Therefore, õit is possible, where scientific validity is unequivocal, for trial protocols to adopt interventions as standard of prevention ahead of national guidelinesö (Haire et al., 2013, p.6). Further, this approach coheres with reciprocal justice rationales expressed by some respondents that participants are deserving of special protection through the provision of services not routinely available, because they endure greater risks than community members through their participation. Indeed, in many countries the standard of prevention implemented in trials deviates from both national policy and services implemented in healthcare settings (McGrory et al., 2010). However, it is unclear how such packages are ensured given the funding restrictions reported in this study and elsewhere (cf. Heise, 2008; MacQueen et al., 2008; Philpott et al., 2010).

In terms of the decision-making criteria of national regulatory approval and public sector availability endorsed by many respondents in this study, this present researcher argues that since regulatory authorities are a protective mechanism (Dawson, 2012; Chilengi, 2009), the endorsement of national regulatory approval is reasonable. However, the requirement that prevention interventions should be available in the public sector ó which is grossly variable according to provincial and urban/rural location ó services the interests of science more than the welfare of trial participants. Varying local standards of prevention complicate what is provided to participants in multi-centre trials. If the local standard is used, it may create differences between participants enrolled in the same trial at different trial sites.

Respondents' distinction between theoretical access (national policy) and actual access (public sector availability) is similar to Haire and Jorden's (2013) assertions that there is often a gulf between written standards of healthcare and the actual reality experienced in healthcare centres, where these standards are not always realised. Therefore, the suggestion that rollout in the public healthcare sector should precede the provision of an intervention to participants in trials, may unduly delay the inclusion of effective interventions in the standard of prevention. Therefore, implementing written standards of prevention (national policy) may result in 'ratcheting up' the standard of prevention in the host community (Jay et al., n.d.; Haire & Jordens, 2013).

4.5 Current versus evolving standards of prevention

This data resonates with concerns already flagged in the literature (Essack, Slack, et al., 2010; Padian et al., 2008) that the standard of evidence for new prevention interventions surpasses what is expected for tools in the current prevention package. Respondents in this study strongly endorsed the ethics guideline recommendation that new tools should be scientifically validated (MRC, 2003; UNAIDS/AVAC, 2011, UNAIDS/WHO, 2012). However, they voiced concern about the vagueness and resultant difficulty of operationalising this requirement (cf. McGrory et al., 2010). Given claims that guidelines are vague, it is unsurprising that prevention interventions are subjected to variable standards of evidence. Few tools in the current standard of prevention have demonstrated conclusive evidence of effectiveness ó more often, the evidence is incomplete or conflicting (Padian et al., 2011). While RCTs are considered the gold standard for establishing the efficacy of interventions, prevention interventions including PEP and STI treatment have not been proved effective in reducing HIV risk in RCTs (Padian et al., 2008). Some respondents conceded that rather than because of their scientific validity, these tools were provided because it was morally

praiseworthy. Practice data also indicated that uncertainty about the scientific validity of an intervention may contribute to poor provider-promotion of such interventions ó at one site it was reported that PEP was provided inconsistently because of provider reservations about efficacy. The potential for provider beliefs to impact on standards of prevention has been previously identified (McGrory et al., 2010).

5. Study limitations and reflexivity

This study adopted a qualitative approach, which allowed for a rich and detailed account of standard of prevention practices, perspectives and complexities. This depth and detail was enabled by the relatively small sample size, and the focus on only two HVTs at South African HVT sites. The data represents a time-limited assessment of practices at five HVT sites and two trials under the umbrella of one research network. The sample was non-random and limited by small sample sizes of CABs ($n=6$), RECs ($n=8$) and site staff at one site ($n_{\text{site3}}=3$). Therefore, the perspectives of these stakeholder groups may not be representative of the full range of possible viewpoints within these stakeholder groups. While efforts were made to sample representatives from sponsor organisations, these interviews did not materialise due to non-response from this stakeholder group to invitations to participate in the study. For these reasons, the representational generalisability (Lewis & Ritchie, 2013) of study findings is limited. Nevertheless, these findings raise a number of critical issues regarding standard of prevention decision-making and implementation in HVTs and the implementation of related norms in ethics guidelines. The themes identified in this research were mostly congruent with previous (albeit limited) empirical research on standards of prevention in other contexts, suggesting that some issues may be experienced in contexts outside South Africa, and in other HIV prevention trials more broadly. Therefore, this research can be argued to be inferentially generalisable (Lewis & Ritchie, 2013). Further, while many of the issues raised could be argued to be context-specific, the fact that South Africa is considered the epicentre of the epidemic suggests that concerns identified in this study could arguably reflect global concerns, and that recommendations may be relevant to other international contexts (Rohleder et al., 2009).

Despite utilising a semi-structured interview guide, the use of a flexible qualitative approach reduced the ability to comprehensively compare data across sites. The various roles, expertise and experience of individual respondents in relation to HVTs also contributed to the range of responses to interview questions. For example, in response to the question ‘could you tell me

about how condoms are provided to participants; one respondent may have included details on condom negotiation skills while another may have not. Since there was no specific question on condom demonstrations and negotiation, it cannot be assumed that if respondents did not raise this, it was not practiced at the site. Similarly, just because a complexity was not identified by a respondent, it does not necessarily mean that it was not experienced at a site. Although qualitative in nature, some of the data in this study may lend itself to quantitative analysis, which may facilitate systematic comparisons of practices across sites and stakeholder groups.

Given the additional ethics review cost and logistical requirements necessary to access trial participants and referral site representatives, these stakeholders were not sampled, even though they were likely to provide an additional perspective on the research questions. Direct observations of HIV prevention services at sites or referral centres were also not undertaken. However, this study's sample and methodology were designed to facilitate critical reflection about prevention services rather than to audit 'end-users'. It was hoped that CAB members, as a proxy for the community, would provide some indication of the experiences of participants. Future explorations on standards of prevention should include the perspectives of trial participants, where feasible, and sponsor organisations and government representatives (including referral service providers), who were identified as key partners in ensuring access to standard of prevention interventions.

Reflexivity entails critical reflection of the research process and the researcher's own role in shaping the collection and analysis of data (Mays & Pope, 2000). In qualitative inquiry, the researcher is considered the primary instrument of data collection and analysis (Merriam, 2002). As such, the possibility of the researcher's influence on respondents' reports of their practices and perspectives was carefully considered.

While the present researcher did not approach the data analysis with preconceived conclusions, particular positions on standards of prevention were preferred; these were developed through previous conceptual research on the topic. Firstly, the researcher agrees with the position that keeping trial participants HIV-uninfected is an ethical imperative in clinical trials of HIV preventive interventions. We have argued elsewhere that certain guideline recommendations set a very high standard and that there are complexities with key HVT-specific guidelines (cf. Essack, Slack, et al., 2010). While some commentators argue

that protecting the welfare of participants should always surpass scientific considerations, these tasks are not always ethically distinct. Rather, it could be argued that when/if adding new tools to the prevention package invalidates trials, then the ethical obligation to provide all state-of-the-art methods is weakened because participants will be exposed to risks and inconvenience for no social benefit and valuable resources will be wasted (cf. Essack, Slack, et al., 2010). The researcher is somewhat sceptical of the feasibility of arguments that the standard of prevention should be the best available in the world but wary of those who contend that it should be on par with local healthcare practice, even if that is nothing. Some of the findings in this study conflict with this researcher's personal perspectives, for example, respondents' endorsement that the standard of prevention be determined by public healthcare availability of interventions. The researcher contends that the standard of prevention should be aligned with written national policy rather than be contingent on public healthcare sector rollout. This will help ensure reasonably commensurate outcomes (cf. Slack, 2014) for participants across various South African sites rather than being subject to the variable access characteristic of the local healthcare sector or the undue delays between research evidence and public sector rollout (e.g., PMTCT, VMMC). Further, the researcher argues that the provision of a higher standard of prevention than that nationally available (e.g., PEP for all risky sexual exposures) is morally praiseworthy but cannot be considered mandatory. While the researcher had spent little time exploring the decision-making aspect of standards of prevention, she had participated in three meetings/workshops on the topic, one of which attempted to develop criteria for making decisions on the evolving standard of prevention (cf. McGrory et al., 2010; Philpott et al., 2011).

As far as possible, the researcher tried not to discuss her personal views with respondents before or during interviews. During interviews, she endeavoured to remain impartial and non-judgemental, although at times exercising empathy through affirmations of respondents' reports, e.g., 'mhmm'. While intended to signify that she was listening to the respondent, such responses may also have been interpreted by respondents as agreement with their perspectives.

At the time this research was conducted, the researcher was employed at an HVT ethics group (HIV AIDS Vaccines Ethics group [HAVEG] <http://www.saavi.org.za/haveg/index.htm>), which conducts research to inform the ethical conduct of HVTs. In this position, the researcher conducted social science research on ethical issues in HIV prevention research.

While the researcher had limited previous direct contact with site staff and other stakeholders, HAVEG was well known among HVT stakeholders, and had close working relationships with sites. Therefore, the researcher's affiliation with HAVEG may have introduced some respondent bias, especially since this research explored practices and perspectives on a controversial ethical issue (cf. Macklin, 2008). In some interviews, respondents' awareness of the researcher's affiliation was apparent. For example, one respondent noted that the researcher was more likely to be knowledgeable about specific ethics terminology and theory while another commented positively on HAVEG's previous work. It is possible that some respondents softened responses regarding their perspectives on ethics guidelines, given that a few respondents conflated HAVEG with guideline developers. Further, this study relied on self-report of HIV prevention decision-making and implementation practices. Self-report, as confirmed by data in the present study, is prone to social desirability bias (Chillag et al., 2006; van de Mortel, 2008). To reduce the potential for social desirability, the study was introduced to sites at a sensitising consultation, where it was emphasised that the study was being conducted in the spirit of critical reflection rather than as an audit. The key aims of this consultation were to: 1) affirm care and prevention responsibilities as a concern shared by many research collaborators including trial sites; 2) hear from site staff and CABs about their prior work, current activities and core priorities around care and prevention in trials; and 3) raise awareness about the proposed study, to identify trial site and CAB concerns about the study, to obtain inputs on the aims, design and outputs of the study and to amend the study, where possible (Essack, Koen & Slack, 2009). Further, data triangulation (interviews and document review), may have circumvented some of this potential bias in respondent reports of practices.

Findings of this study that cultural norms may restrict the discussion of sex-related issues in the presence of women, raised the possibility that such norms may have played out in interviews. As a female researcher, some male CAB respondents may not have fully disclosed their perspectives and practices on certain HIV prevention issues. Despite the potential for these biases, respondents appeared generally unguarded in presenting their practices and perspectives.

As explicated in the methodology chapter (Chapter 6), a critical thematic approach to data analysis was adopted, enabling a descriptive, critical and interpretive analysis of the data. This approach to the analysis and interpretation of results cannot be considered definitive,

given that different approaches are likely to yield different interpretations of the data. Specifically, due to limited philosophical expertise, the researcher was unable to undertake a moral philosophical analysis of standards of prevention, which might have provided a useful adjunct to this social science analysis or served as a useful lens through which to interpret the data. Readers are referred to Haire (2013) for a detailed normative analysis related to determining standard of prevention packages for HIV prevention trials, specifically regarding PrEP.

6. Summary

This chapter discussed four overarching themes identified in respondents' reports of their practices and perspectives on standards of prevention. It aimed to provide a deeper interpretation of data through contextualising findings within the larger body of literature and in relation to relevant normative frameworks.

In terms of theme 1, '*dynamics of standard of prevention decision-making and implementation*', findings suggested that gender and cultural norms impacted on standard of prevention decision-making and implementation. Cultural taboos about discussing sex in certain groups impeded some CAB input into the design of prevention interventions. It also impacted on self-report practices, and ultimately on participant uptake of prevention interventions. The gender gap between access to male and female condoms at sites and in the public sector may have several potential negative consequences for uptake of this important female-initiated intervention. Power dynamics were observed in all phases of HVTs, from protocol development to implementation. These inequalities evoked 'othering' discourse, which in turn complicated the ethical ideals of collaboration on standards of prevention.

Theme 2, '*defining the standard of prevention through consultation, consensus, and negotiation*' identified the perils of these decision-making mechanisms recommended in guidelines, including that inherent power dynamics between and within stakeholder groups may compromise the consultative and intended inclusive nature of standard of prevention decision-making. Given observed power differentials, this study also questioned the suitability of presently recommended mechanisms for standard of prevention decision-making.

Theme 3, *ensuring access to HIV prevention interventions: sourcing funding and establishing partnerships*, captured findings which suggested that funding complexities pervaded both the design and implementation of the prevention package, and had implications for current and evolving standards of prevention. Given complexities with funding, South African sites developed strategic partnerships with government stakeholders (DoH) and other partners to ensure access to prevention interventions.

Theme 4, *'double standards of prevention'*, discussed findings that double standards existed beyond the pre-occupation with ensuring parity between developed and developing countries. Concerns included variability in decision-making about current versus evolving standards of prevention; requiring national regulatory approval before adding a new method to the prevention package; deviations between stakeholder practices and perspectives; and the potential for differences in standards of prevention both within and across trial sites in the same country.

CHAPTER 12

CONCLUSIONS AND RECOMMENDATIONS

As new prevention tools are proven effective, the standard of prevention in HIV prevention trials is becoming an increasingly complex and divisive ethical issue (Macklin, 2008; Moorhouse et al., 2014). Ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) make a range of recommendations about the standard of prevention, including that participants should be provided with access to all “state-of-the-art” prevention interventions; that details of risk-reduction interventions should be included in protocols and consent forms; and that standard of prevention decisions should be made in consultation with relevant stakeholders. These recommendations have been described as setting a very high substantive and procedural standard (Essack, Slack, et al., 2010; HPTN, 2009; Macklin, 2009), and as impractical and infeasible, particularly in resource-constrained contexts (Macklin, 2010).

This study responded to calls by commentators to document standard of prevention practices at sites (Essack, Slack, et al., 2010), and assess the extent to which actual practices (what *is* happening) corresponded with ethics guidance (what *ought* to be happening according to norms) (Macklin, 2010). While recent research (Haire & Jordens, 2013; Heise et al., 2008; Ngongo, Priddy, et al., 2012) has explored the standard of prevention in HIV prevention trials, there has been no detailed exploration of standard of prevention practices in South African HVTs, nor efforts to comprehensively compare practices with recommendations in ethics guidelines. The current study aimed to address this gap.

By documenting decision-making and implementation practices in South African HVTs, this study hopefully contributes to existing empirical data on standards of prevention in HIV prevention trials. By evaluating the congruence or difference between stakeholder practices and related ethical standards in guidelines, this data responds to debates about the implementability of these ethical standards (cf. HPTN, 2009; Macklin, 2009; 2010; Moorhouse et al., 2014). By exploring complexities in actual standard of prevention practices and examining resonance with ethics guidelines, this research identifies areas where site practices and ethics guidelines could be strengthened. In this way, this study was careful to interrogate practices and norms equally, operating under the assumption that practice can

inform ethical theory just as ethical theory can inform practice (Frith, 2008). Empirical accounts of ethical issues not only help to identify novel ethical complexities but also help to develop moral norms and theories that are responsive to issues identified on the ground (Caplan, 1982). By seeking stakeholder perspectives on key standard of prevention ethics recommendations, this study may help distinguish between functional norms (those extolled and implemented in practice) and non-functional norms (those extolled but ignored) (Reese & Fremouw, 1964). Further, it may also indicate which norms in guidelines are not extolled but implemented, or not extolled and not implemented. Finally, data on standard of prevention decision-making and implementation complexities are also likely to be of value to trial implementers planning and conducting future HIV prevention trials.

This chapter presents an overview of the main study findings, conclusions and recommendations.

1. Key study findings

1.1 Actual practices versus ethics norms

This study aimed to explore the correspondence between standard of prevention decision-making (Chapter 7) and implementation (Chapter 9) practices with related recommendations in ethics guidelines.

1.1.1 Standard of prevention decision-making

Decisions about which prevention components to include in the standard of prevention package were made primarily by the protocol committee during protocol development. These decisions were vetted by RECs and CABs during the review process. Therefore, key research stakeholders (sponsors, research networks, investigators, RECs and community representatives) were engaged in standard of prevention determinations, as recommended by ethics guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Community engagement practices at sites resonated with ethics recommendations to involve community representatives in protocol development and review, and to build their capacity to make decisions. Challenges in ensuring meaningful community engagement reported in this study reflected pragmatic and logistical constraints, and the need for improved research literacy, rather than disagreement with norms requiring community engagement. However, given the reported complexities with involving representatives of all sites (investigators and CABs) on

protocol development committees, in practice, engaging *all* research stakeholders on *all* standard of prevention decisions appeared to be impractical in this context.

There was a difference in the standard of prevention outlined in the phase I and phase IIB protocols, indicating that protocol writers may have accorded different obligations to early- and late-phase trial participants, based on their perception of participants' risk of HIV infection. Ethics guidelines do not specify whether the obligation to provide prevention services differs according to the phase of the trial or vulnerability of participants.

In practice, agreement between stakeholders on the prevention package was not sought prior to commencement of the HVTs, nor was a process of formal negotiation utilised to determine components of the prevention package. Therefore, reported practices did not cohere with recommendations for consensus (UNAIDS/WHO, 2012) and negotiation (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) on the standard of prevention package.

The range of perspectives on the substantive standard indicate that there is little consensus on standards of prevention, including regarding fundamental concepts like 'state-of-the-art' and 'scientific validity'. This data corroborates criticisms of consensus identified in the literature (Essack, Slack, et al., 2010; London & Zollman, 2010; Schüklenk, 2010; Slack & Stobie, 2010) and concludes that given the vagueness of guidelines and the absence of clear operational frameworks, recommendations to agree on the standard of prevention, prior to the implementation of each trial (UNAIDS/WHO, 2012) are not currently feasible in this context. While this study did not evaluate the pragmatic value and implementability of currently available frameworks for decision-making (e.g., Jay et al., n.d.; McGrory et al., 2010; Philpott et al., 2011; Tarantola et al., 2007), this study has provided empirical data identifying the critical need for such frameworks to be piloted, evaluated, and if necessary refined.

1.1.2 Standard of prevention implementation

The HVTs in the present study provided participants with risk-reduction counselling and access to male and female condoms and STI treatment (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) as well as VMMC and PEP, where indicated (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), in accordance with ethics guideline recommendations. However, inconsistent access to female condoms at most sites suggests that the obligation to ensure access to female condoms was not wholly fulfilled. In some instances, site practices exceeded

recommendations in guidelines, for example, by paying for VMMC at private facilities and by providing assisted referrals to participants or partners. Site services also sometimes exceeded preventive options available in the local community, for example, by ensuring access to PEP for all sexual exposures, and to VMMC at a time of limited public sector access. This indicates that, in the setting in which these data were collected, ethics recommendations to ensure access to state-of-the-art services were achievable, and in some cases exceeded. However, this finding may not hold as the state-of-the-art evolves since it may become increasingly difficult ó scientifically and logistically ó to ensure access to state-of-the-art interventions.

This study found that in practice, the burden of ensuring access to prevention interventions is shared among sponsors, research networks, researchers, host governments, and in some instances private donors, in congruence with guideline (UNAIDS/WHO, 2012) recommendations. The availability of funding and establishment of strategic partnerships affected standard of prevention determinations and were critical factors in ensuring access to prevention interventions. However, the bulk of the responsibility to ensure access to prevention interventions was assumed by research networks, researchers and the host government, with sponsors making a nominal contribution due to funding policy restrictions. Ultimately, the package of prevention implemented in HVTs was dependent on several factors, including donor funding policy, securing alternate funds, the prevention interventions available locally, the partnerships established, and available site resources.

This study found that South African HVT implementers favoured the more onerous direct provision of prevention interventions over referral (access). However, whether prevention interventions were provided on-site or via referral was contingent on the available funding and the nature of established partnerships ó as a procurement source or a service provider.

This study found that in practice, sites provided substantially more to participants than was specified in consent documents for both trials and in the phase I trial protocol. REC and CAB practices for the review of protocols were largely consistent with ethics guideline recommendations (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012), except for the requirement that RECs approve plans for monitoring risk-reduction interventions ó such plans were not included in study protocols or ethics applications. Therefore, ethics

recommendations for protocol drafting and review, and ethical oversight of standards of prevention were only partially achieved.

1.2 Responsiveness of ethics guidelines to standard of prevention complexities

Ethics guidelines anticipate some of the core thematic complexities raised by stakeholders. As predicted by guidelines (UNAIDS/AVAC, 2011), in practice, sponsor funding restrictions had implications for the provision of prevention services. However, respondents raised critical concerns that a lack of clear sponsor funding policies may enable sponsors to renege on their ethical obligations to help keep trial participants HIV-uninfected.

Guidelines anticipate the potential for power inequalities in research and provide several remedial strategies (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). This study provides empirical evidence of how such concerns play out in practice. Power pervaded all stages of HVT decision-making from protocol development, where sponsors were perceived as commanding decision-making authority, to protocol implementation, where deference to the perceived authority and expertise of providers may have mediated participant uptake of services. While guidelines recognise the potential for power imbalances, they recommend negotiation and consensus as mechanisms for standard of prevention decision-making. However, the premise of negotiation rests on the assumption that the negotiating parties are, for the most part, equal partners (cf. UNAIDS/AVAC, 2011). Given the power inequalities reported in this study, and that power pervades all facets of negotiation (Cheng, 2009), this study questions whether negotiation is the most appropriate mechanism for standard of prevention decision-making.

The assessment of correspondence between practices and guidelines also identified which empirically-identified concerns were not anticipated by guidelines.

This study identified the novel perspective that cultural prescriptions may limit community inputs into the design and review of standards of prevention. Findings also indicated the potential for gendered prevention practices. For example, in practice there was a gender gap in the provision of condoms, with female condoms only intermittently available and subjected to restrictive dispensing practices. Guidelines do not anticipate that socio-cultural taboos may hinder community inputs into standard of prevention determinations nor that the

promotion and uptake of prevention interventions may be influenced by cultural and gender norms.

The potential for so-called double standards (Macklin, 2004; 2009; Haire et al., 2013) exists beyond predominant concerns about ensuring equitable outcomes for participants in developed and developing country contexts. Stakeholder perspectives highlighted the lack of normative clarity on key concepts like ‘state-of-the-art’, ‘scientific validity’ and ‘approval by relevant bodies’. Ill-defined and broadly worded guidelines (Haire, 2013; Moorhouse et al., 2014) create normative ambiguities and may inadvertently perpetuate differences in the implementation of standards of prevention. HVT stakeholders might therefore experience uncertainty about whether the ‘state-of-the-art’ should be benchmarked against international or national standards (Dawson et al., 2014) and whether regulatory approval is required of national or any authorities (Haire, 2013).

Given the multiple factors found to impact on standard of prevention decision-making and implementation, within-country differences in standards of prevention between trial participants are possible, and were reported in this study. While the flexibility to determine standards of prevention on a site-by-site basis was valued by some stakeholders and supported by guidelines, such practices may also create site-level differences.

Standards of prevention may differ between trials at one trial site, and within trials across different sites, raising concerns about fairness if participants are exposed to the same level of risk but receive different benefits. The potential for such differences in prevention outcomes for participants within one country is not anticipated in guidelines.

Empirical data from this study have illuminated the internal conflict in guidelines between substantive norms requiring access to state-of-the-art prevention interventions, and procedural norms recommending negotiation of the prevention package. Guidelines provide little direction on how to resolve tensions which result when procedural outcomes conflict with substantive norms, except that implementation practices should not compromise fundamental substantive ethical standards (MRC, 2003). In practice, stakeholders endeavoured to meet substantive norms to provide counselling and access to state-of-the-art prevention interventions in HVTs trials. However, they have largely failed to implement

procedural recommendations for consensus and negotiation in determining the prevention package.

1.3 The evolving standard of prevention and perspectives on norms in ethics guidance

Finally, this study explored stakeholder practices and perspectives on the evolving standard of prevention (Chapter 8) and perspectives on selected standard of prevention recommendations in ethics guidelines (Chapter 10).

The addition of VMMC to the prevention package identified differences between stakeholder practices and perspectives. VMMC was added to the prevention package based on scientific validation determined by evidence from three clinical trials and *prior* to its endorsement by national bodies or the development of national guidelines for use (cf. Haire & Jordens, 2013). Stakeholder perspectives however, reflect endorsement of scientific validity (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) *and* approval by national regulatory authorities (UNAIDS/AVAC, 2011). Further, these findings indicated some endorsement of additional criteria of availability in the public healthcare sector and the phase of the trial, which are not explicit requirements of guidelines (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). Stakeholders in this study did not spontaneously endorse stakeholder consultation as a mechanism for the enhancement of the standard of prevention. While stakeholder perspectives are not morally definitive, the data suggest challenges with implementing consultation recommendations in practice, including regarding which stakeholders should be consulted and when, and what format consultations should take (Moorhouse et al., 2014). Guidelines do not prescribe appropriate consultation formats; however, some respondents considered the process of developing and reviewing the protocol as a legitimate consultative mechanism. Since protocols are developed by the protocol committee (with representation, albeit nominal, from all stakeholder groups) and reviewed by national regulatory authorities, RECs and CABs, the present researcher agrees that protocol development and review may serve as one mechanism of stakeholder consultation.

The addition of VMMC demonstrated that adding new prevention tools that are not available in the public sector presented challenges when donor funding policy also precluded their provision. This study found that establishing partnerships with private donors was an

effective strategy in ensuring access to interventions not yet incorporated in national policy or not rolled out in the public sector.

2. Recommendations

This empirical study on standards of prevention in South African HVTs, considered norms, perspectives and practices on standards of prevention. Specific recommendations for norms, practices and future research are detailed in Appendix 9. The following section considers recommendations in relation to major study findings.

2.1 Recommendations for future research

This study identified the tension experienced by some CAB respondents (and potentially host communities) when socio-cultural taboos about discussing sex (cf. Ndinda et al., 2011) intersect with ethics guideline recommendations for input into standards of prevention. Further, findings suggested the potential for gender/cultural norms and stereotypes to impact on the design, accessibility, promotion and uptake of prevention interventions. More detailed research that clarifies the extent to which gender norms and cultural prescriptions influence the realisation of recommendations in ethics guidelines should be undertaken. Innovative strategies for facilitating CAB inputs into standards of prevention without compromising cultural ideologies should be developed and tested.

Further, as new tools (e.g., PrEP) are added to the prevention package, trials will become increasingly expensive to conduct (Haire et al., 2013). Even though the cost of providing prevention interventions may not be borne by sponsors themselves, the willingness of sponsors to accommodate increasing costs as a result of longer and larger trials necessitated by enhanced standards of prevention, needs urgent exploration.

Given the paucity of evidence supporting consultative decision-making processes for standards of prevention, and indications of the difficulty implementing these recommendations in practice, future research should pilot and evaluate existing frameworks that propose procedural decision-making processes (e.g., Tarantola et al., 2007) that take into account some of the challenges with consultation reported in this study. Further, stakeholder perspectives on the value of frameworks (e.g., Jay et al., n.d.) that attempt to offer operational guidance on when to add new methods to the prevention package, should be explored. The

pragmatic value of such frameworks for trial implementers could also be determined through piloting exercises.

As new prevention tools emerge, a critical gap in knowledge remains regarding the threshold at which adding new methods will invalidate trials. Protecting the welfare of participants necessitates the provision of all prevention methods (Haire, 2013; Macklin, 2010; UNAIDS/WHO, 2012; UNAIDS/AVAC, 2011). However, if the feasibility of obtaining meaningful results from the trial is adversely impacted by the addition of new HIV prevention methods, then the ethical obligation to provide all state-of-the-art methods is weakened because participants will be exposed to risks and inconvenience for no social benefit and valuable resources will be wasted (Emanuel et al., 2004; Essack, Slack, et al., 2010). Therefore, defining the threshold at which adding new tools invalidates trials, remains an important ethical undertaking (Essack, Slack, et al., 2010).

2.2 Recommendations for ethics guidelines

This study aimed to make recommendations for ethics guidance.

Complexities associated with power dynamics identified in this study suggest that ethical recommendations to negotiate standards of prevention may be compromised by power inequities. Guidelines should therefore carefully consider alternative mechanisms for standard of prevention decision-making, which are constructive and engender collaboration rather than opposition (us versus them). To minimise the potential for procedural outcomes to conflict with substantive norms, consideration should be given to implementing procedural recommendations only in those circumstances where the proposed prevention package deviates from the substantive standard or accepted practice. Further, rather than establishing a ceiling (all state-of-the-art) and allowing that it be lowered through negotiation under prescribed conditions, consideration could be given to establishing a minimum core standard of prevention, and ratcheting it up. In this way, procedural outcomes would not conflict with the substantive norms.

Findings about perceived complexities regarding provider-promotion and participant uptake suggests that guideline recommendations to monitor the quality of prevention interventions should be refined to recommend oversight and/or monitoring of both promotion and uptake.

One of the key criticisms (Koen et al., 2013; Moorhouse et al., 2014; Philpott et al., 2011) of guideline recommendations on standards of prevention was that fundamental concepts (e.g., ‘state-of-the-art’, ‘scientific validity’, ‘consultation’, ‘approval by relevant bodies’ and ‘research stakeholders’) were considered too vague, creating complexities with interpreting and operationalising these recommendations in practice. In the absence of clarity, stakeholders in this study favoured a ‘state-of-the-art’ interpreted as the best available in the country and endorsed national regulatory approval as a criterion for the addition of new prevention tools. Further, findings from this study that RECs applied variable standards in reviewing protocols overlap with concerns about the variability of REC decisions in multi-site clinical trials (Shah, Whittle, Wilfond, Gensler, & Wendler, 2004). This suggests that RECs need clearer substantive and procedural guidance on how to review standards of prevention. These findings echo recommendations from a parallel quantitative study that guideline developers should consider clarifying vague concepts (Moorhouse et al., 2014) or develop a clearer guidance point (both in terms of substantive and procedural norms). Alternatively, if guideline developers opt to maintain broadly phrased recommendations, resources and operational frameworks should be developed as an adjunct to guidelines (Moorhouse et al., 2014).

While recommendations to aspire to state-of-the-art prevention services were intended to minimise so-called double standards between developed and developing countries (Haire et al., 2013), the present empirical data indicate the potential for different standards between participants enrolled in different protocols and/or at different sites. Further, findings showed that between-site differences may be enabled by certain guideline assertions, e.g., that protocols may vary in ‘modes of delivery’ for prevention interventions (UNAIDS/WHO, 2012, p. 45) and that standard of prevention negotiations occur on a trial-by-trial basis (MRC, 2003; UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012). This suggests that ethics guidelines will need to address the issue of different standards between trials implemented within the same site or between sites within the same country. For example, guideline developers could refer to the first version of GPP guidance (UNAIDS/AVAC, 2007) which recommended that trial sponsors should ensure that core elements of the prevention package are consistent across trials and networks.

While guidelines are generally silent on whether the obligation to provide prevention services may or should differ according to the phase of the trial or risk-level of participants, these data

indicated that protocol-writers, and some stakeholders in this study, assigned different standard of prevention obligations for early-phase versus late-phase trial participants. Given that risk may be related to the study product (Gray et al., 2010; Halpern et al., 2008; van Damme et al., 2002) and not only the risk behaviour of participants, guidelines should consider clarifying whether obligations to participants differ based on trial phases/risk-levels.

Practice data also identified that sites endeavoured to provide prevention interventions to persons not enrolled in trials. However, guidance is unclear on the standard of prevention for those not enrolled in trials (Tarantola et al., 2007). Future revisions should be clearer on what, if anything, should be ensured for those not enrolled in trials.

2.3 Recommendations for stakeholder practices

This study aimed to make recommendations for improved stakeholder practices.

Data in this study suggested a perception that standard of prevention decision-making occurs in a top-down manner, given that protocol development is a fairly centralised activity and that CAB and REC review occur concurrently, raising concerns about tokenistic CAB engagement. This confirms previous reports (Hannah et al., 2012; Ngongo, Hannah, et al., 2012), that there are gaps between GPP guidelines (UNAIDS/AVAC, 2011) and actual practices of stakeholder engagement in protocols and standards of prevention. Given concerns about how CAB representatives were selected for protocol development committees, it is recommended that the research network, trial sites and CAB representatives should explore alternative mechanisms to enable stakeholder inputs on standards of prevention. One possibility may be to encourage a CAB representative at each site to serve on RECs reviewing HIV prevention trial protocols. As statutory bodies for the ethical oversight of research, RECs may also be well placed to request that sites document efforts (and challenges) in meeting requirements in GPP guidelines (UNAIDS/AVAC, 2011).

Reported complexities with the implementation of prevention interventions may be relevant as new prevention methods, e.g., PrEP and microbicides, become accepted as part of the standard of prevention. Data in this study reflecting challenges in funding certain prevention interventions suggest that sponsor restrictions on how funding can be utilised need to be revisited (Philpott et al., 2010) in a way that satisfies ethical responsibilities to ensure access to prevention interventions. It is recommended that sponsors clarify their funding policies and

develop a more formal policy on standards of prevention, in collaboration with HVT stakeholders. Given the potential for reduced funding in future trials and the cost implications of enhanced prevention packages, trial implementers should make efforts to diversify funding sources and carefully consider the partnerships that need to be established to enable access to upcoming prevention tools, for example, to procure products for on-site dispensing, or to establish innovative referral relationships.

As new prevention interventions become standard of prevention, the role of partnerships to ensure access to prevention interventions becomes increasingly important given the potential for sponsor funding restrictions. The DoH emerged as a key partner in ensuring access to many prevention services. However, engaging this partner was associated with some tensions, for example, poor accessibility of female condoms. Data in this study describing tensions related to engaging key partners suggest that new sites should engage critical stakeholders in an early, sustained and strategic manner. It also suggests the usefulness of ongoing evaluation of the quality of key partnerships. Sites should also capitalise on targets set in the NSP to increase access to female condoms to 20 million by 2016 (SANAC, 2011). Nevertheless, given that the gap in distribution between male and female condoms appears to be widening prospectively (500 million male condoms and 9 million female condoms to be distributed in 2012 versus 1 billion and 20 million respectively to be distributed by 2016) (SANAC, 2011), investigators should lobby HIV prevention activist groups in advocating for improved access to female condoms. If HVT stakeholders, including the South African government, are to meet their obligations to protect the vulnerable, increasing access to female condoms must be ensured. Further, sites should be cautious about the consequences of relying on partnerships to ensure access to prevention interventions that may subject them to gender, cultural or political barriers set by the state.

Given this study's findings that site staff promotion of some prevention interventions may be adversely impacted by the cultural context and perceptions of the efficacy of the intervention, sites should consider implementing formal mechanisms to assess provider-promotion of prevention services and to train staff to ensure consistent promotion. Strategies should be developed to identify, interrogate and respect objections to uptake from certain sub-groups based on values and preferences.

Findings also indicated that consent forms contained fewer disclosures about prevention options than were actually provided to participants. While the information sheet and consent form is only part of the informed consent process (Flory & Emanuel, 2004), given that participants may use the consent form for reference purposes (Ramjee et al., 2010), it is recommended that they contain more information on the standard of prevention.

Alternatively, an additional fact sheet on standards of prevention could be provided to participants. This may also help counter potential variability in provider-promotion of services. More detailed disclosures in consent forms should, where possible, preserve site flexibility in implementing prevention services. Given their important role in the ethical oversight of research, it is imperative that RECs and CABs review the actual versus the written standard of prevention for all trials. These findings support the recommendation by Heise et al. (2008, p. 67) that all trials should explicitly define standards of care that will be provided at each trial site; the broad elements of care can be described in the protocol, while specific elements can be written into site standard operating procedures.

2.4 Recommendations for capacity building

This study found gaps in socio-cultural, research (cf. UNAIDS/AVAC, 2011) and ethics competencies. While site staff were fairly knowledgeable about the socio-cultural context in which they conducted trials, they did not anticipate that cultural prescriptions may impede CAB inputs into the design of prevention interventions or that female condoms would present gendered challenges. This underscores the pivotal importance of understanding the norms, practices and beliefs of relevant local cultures to inform the development of appropriate trial designs and procedures (UNAIDS/AVAC, 2011, pp. 22-23).

Further, findings from this study indicated that CAB knowledge of both substantive and implementation issues on the standard of prevention was inadequate. While many of the CAB respondents could detail their concerns regarding issues of HIV care and treatment, the standard of prevention was not consistently noted as a concern by CAB respondents nor was it described as a critical element of the review process. Further, a lack of research literacy and understanding of science appeared to have impeded protocol review. To ensure effective decision-making, CABs need ethics and research literacy training so that they are able to critically evaluate study protocols and actively engage with the research. This underlines the importance of continuously engaging in intensive efforts to build research competency, which enables and empowers stakeholders to provide meaningful input into the research process

and enhances understanding of the concepts, purposes, practices, limitations, and results of biomedical HIV prevention trials (UNAIDS/AVAC, 2011, p. 23). More use could be made of specific funding opportunities (e.g., Wellcome Trust's 'Public Engagement with Health Research'¹³, the European and Developing Countries Clinical Trial Partnership (EDCTP)¹⁴, and European Union (EU), 'Science and Society'¹⁵) to fund the building of such capacity, unless additional HVT sponsors are earmarked for such engagement.

Variability in the review of HVT protocols by RECs suggested variable research ethics capacity (among other issues), which limited the ability of RECs to interrogate major substantive issues, such as standards of prevention. In line with NHREC guidelines that REC members receive initial and ongoing research ethics training (Cleaton-Jones & Wassenaar, 2010), RECs could benefit from intensive ethics training including on mechanisms to enhance their interrogation of substantive ethical issues. The lack of accessibility, awareness and understanding of HVT-specific ethics guidelines also emphasises the need to build ethics competency among all HVT stakeholders as a matter of priority.

3. Conclusion

This thesis aimed to explore standards of prevention in South African HVTs in order to provide insight into actual practices at sites in relation to standard of prevention norms in guidelines. It highlighted areas where practices were congruent with (and exceeded) guideline recommendations, where they deviated from guidance, and whether guidance provides useful direction to stakeholders in addressing on the ground complexities.

South African HVT stakeholders are endeavouring to meet their obligations to protect trial participants and help them remain HIV-uninfected. Despite concerns that ethics guidelines set the bar high (Essack, Slack, et al., 2010; HPTN, 2009; Macklin, 2009) and may be infeasible, especially in resource-constrained contexts (Macklin, 2010), this study found that in the main, there was a commendably high degree of correspondence between actual practices at South African HVT sites and related recommendations in ethics guidelines. However, points of deviation between guidelines and practices have elucidated that we need improved guidance, strengthened practices and better oversight capacity if we are to fully ensure the

¹³ <http://www.wellcome.ac.uk/Funding/Public-engagement/index.htm>

¹⁴ <http://www.edctp.org/calls-and-grants/>

¹⁵ <http://ec.europa.eu/research/science-society/index.cfm?fuseaction=public.topic&id=1241>

well-being of trial participants. It is hoped that these empirical findings will usefully inform and enhance normative debate on standards of prevention and also contribute practical solutions to addressing complexities experienced in practice.

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Appendix 1: Standard of prevention norms in HVT-specific ethics guidelines

Term	Abbreviation
Care	Cx
Prevention	Prevention
Risk-reduction counselling	RRC
Risk-reduction interventions	RRIs
Treatment	Rx
Standard of prevention	SoP
Trial participant	TP

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
<p>1.</p> <p>Who should receive prevention methods?</p> <p>Screen-outs, partners, families & the community</p>	<p>The research protocol <i>should</i> specify referral processes for those persons excluded from the trial, where relevant (GP4, Research protocols & study populations, p. 9).</p> <p>Participants should be informed how to obtain (STI) Rx for their partners (GP 14, HIV RRI, p. 29)</p> <p>Sponsors & investigators should build capacity of trial linked healthcare centres to deliver services to the host community, & ensure that there is a contribution of lasting benefit to host communities (bolded GP 16, Rx & Cx, p. 31)</p>	<p>Ways <i>should</i> be explored with local authorities to provide trial volunteers & participants with information about HIV Px & Rx services available in the community (GP 13, SoP, p. 46).</p> <p>Clinical trials <i>should</i> be integrated into national Px, Rx, & Cx plans so that services provided through clinical trials or arrangements brokered for TPs serve to improve the health conditions of both the TPs & the community from which they are drawn, & (to) support & to strengthen a country's comprehensive response to the epidemic (GP 14, Cx & Rx, p. 49-50).</p> <p>There should be an ongoing</p>	<p>Research teams & relevant stakeholders discuss & negotiate the comprehensive HIV prevention package, taking account of the following:</p> <ul style="list-style-type: none"> The HIV prevention services that will be available to partners of trial participants. (Standard of HIV prevention, p. 51) 	<p><i>In addressing what should be provided to screen-outs, components not specified. Perhaps the lack of guidance on Px services for screen-outs is that most volunteers may not meet enrolment criteria because they are already infected → HIV Px not required & positive Px is dealt with under Cx & Rx.</i></p> <p><i>GPP has the clearest statement on services for partners.</i></p> <p><i>Only MRC (2003) specifies the mechanism for accessing services for screen-outs & this is limited to referral.</i></p>

Dimension	MRC (2003) HIV Preventive vaccine research. Book 5	UNAIDS (2007). Ethical considerations	UNAIDS-AVAC (2011) Good Participatory Practice (GPP)	My notes: Across guideline analysis
		iterative consultative process to facilitate local or national decision-making about the appropriate level of support, Cx, & Rx provided to potential & enrolled participants (GP 12, Benefits, p. 43)		
My notes: Within guidelines analysis	<p><u>General support & services not specific to Px:</u> Statement on referral for screen outs. Implies that screen-outs get the standard available in the local healthcare system. Also a statement that capacity should be built to deliver services to host communities.</p> <p><u>Px-specific:</u> Does state that TPs be informed about where partners can be treated for STIs, but no detail on whether this Rx will be offered at the site or through the local healthcare system. Screen-outs & partners</p> <p>Covers all levels of the 'who' specified in the good governance model.</p>	<p><u>General statement</u> in Cx section that support should be provided to potential participants.</p> <p><u>Px-specific:</u> trial volunteers should be provided with info on the HIV px services available in the community; the health conditions of the community should be improved. How? By integrating clinical trials into national prevention plans.</p> <p>Revisions should include a clearer statement on what components of prevention should be provided to those who screen out, if anything</p> <p>Screen-outs & the host community</p> <p>Only covers three levels of the 'who' specified in the good governance model, i.e. TPs (see below), screen-outs & host community. Does not "other persons linked to trial participants but not considered for enrolment,</p>	There should be discussion & negotiation about the prevention services that will be available to partners of TPss. Nothing on screen outs or the wider community.	The good governance model requires that stakeholders consider 'who' should get services: trial participants, screen-outs, family/partners, host community

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
		<i>e.g. family members or sexual partners"</i>		
<p>2.1. What should be provided to participants?</p> <p>The substantive standard</p>	<p>The most appropriate RRC & <i>access</i> to preventive methods <i>should</i> be <i>provided</i> to all TPs (GP 14, RRs, p. 28: bolded GP).</p> <p>Investigators are morally compelled to <i>provide</i> optimal risk-reduction measures to TPs (GP 14, RRs, p. 28).</p> <p>Every effort <i>must</i> be made to <i>provide</i> participants with optimal RRC & interventions to prevent HIV infection (GP 9, Potential harms, p. 17)</p>	<p>Researchers, research staff, & trial sponsors <i>should</i> ensure that appropriate counselling & <i>access</i> to all state-of-the-art HIV risk-reduction methods are <i>provided</i> to participants through-out the trial (GP 13, SoP, p. 45, bolded GP).</p> <p>Protocols for HIV Px research <i>obligate</i> researchers to <i>provide</i> the full range of information & services for risk-reduction... If researchers can't guarantee this standard, it is unethical to conduct the trial (GP 13, SoP, p. 45).</p> <p>All TPs <i>should</i> receive HIV RRC, as well as access & <i>entitlement</i> to proven Px methods, & to post-exposure prophylaxis in the event of a known likely exposure (GP 13, SoP, p. 46)</p> <p>Some of the activities related to the conduct of HIV biomedical HIV Px trials which may benefit those who participate may actually be rights. At a minimum, participants should:...receive comprehensive information regarding HIV transmission</p>	<p>The term "standard of HIV prevention" refers to the package of comprehensive counselling & state-of-the-art HIV risk-reduction methods provided or made available to participants in biomedical HIV prevention trials (Standard of HIV px, p. 48).</p>	<p><i>There is fairly good consistency in the 3 guidelines in terms of the substantive standard – TPs should receive optimal/ state-of the art risk-reduction methods. However, EC seems to set the highest substantive standard. If this standard can't be achieved then it is not ethical to conduct the trial.</i></p>

Dimension	MRC (2003) HIV Preventive vaccine research. Book 5	UNAIDS (2007). Ethical considerations	UNAIDS-AVAC (2011) Good Participatory Practice (GPP)	My notes: Across guideline analysis
		& how it can be prevented; receive access to HIV testing & Px methods, including male & female condoms, sterile injecting equipment, & sexual & reproductive healthcare services...(GP 12, Benefits, p. 44)		
My notes: Within guidelines analysis	<p>Advocates an OPTIMAL package but does not state that “all” preventive methods should be provided.</p> <p>The meaning of the term “appropriate” is not clear.</p> <p>Requires that investigators provide TPs with preventive methods.</p>	<p>Advocates a STATE OF THE ART package & specifies that “all” state of the art HIV risk-reduction measures are provided.</p> <p>The meaning of the term “appropriate” is not clear.</p> <p>Requires that researchers & sponsors ensure that preventive methods are actually provided to all TPs → very high standard (Macklin, 2009).</p> <p>Requirement to provide all state of the art methods has been criticised as setting too high a standard (cf. HPTN, 2009).</p>	<p>Advocates for STATE OF THE ART HIV risk-reduction methods.</p> <p>No substantive statement.</p> <p>Requires that HIV px methods are provided <u>OR</u> made available</p>	<p>Optimal or state of the art</p> <p>EC & MRC state that access should be provided GPP states that Px methods are provided OR made available</p> <p>Only EC requires that ALL state of the art methods should be provided. Little clarity on what exactly is state-of-the-art. According to Tarantola et al. (2007) standards in ethical guidelines provide little practical guidance. They do not specify the type, level & duration of prevention. However, good governance as an outcome aims to ensure compliance with international & national scientific & ethical standards which would mean that all prevention services should be provided to trial participants & consulting on what to provide would be illogical.</p>
2.2.	In GP 14, RRI, p. 29.	In GP 13, SoP, p. 45-46.	All scientifically validated methods	Components of packages are fairly

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
<p>What should be provided to participants?</p> <p>The components of the package</p>	<ul style="list-style-type: none"> • methods to decrease risk of HIV infection • comprehensive RRC <p>Preventive methods should include (but not ltd to):</p> <ul style="list-style-type: none"> • Basic principles of risk-free & safer sexual practices • Education concerning general health & identification & Px of STIs; • Appropriate access to barrier methods, such as condoms & info about where barrier methods are locally available • Rx of STIs & info about how partners can be treated • Counselling around the potential benefits & risks of PEP & how it can be accessed 	<ul style="list-style-type: none"> • proven Px methods & PEP; • Counselling • Appropriate access to male/female condoms; • Rx for other STIs. • Provision for family planning, pregnancy, childbirth services • Sterile injecting equipment & medical substitution therapy; <p>Counselling should include:</p> <ul style="list-style-type: none"> • Basic principles of safer sexual practice & safer injecting practices • Education concerning general health & Rx of STIs • The potential benefits & risks of PEP & how it can be accessed. • Reproductive health, contraception pregnancy Cx etc. • Strategies to reduce domestic violence <p>Protocols for HIV Px research obligate researchers to provide the full range of information & services for risk-reduction, although they vary in defining the package of services & modes of delivery (GP 13, SoP, p. 45).</p>	<p>are discussed, & their appropriateness for the trial design & population assessed, including:</p> <ul style="list-style-type: none"> • Risk assessment & risk-reduction counselling—including partner & couple counselling. • Male & female condoms—with appropriate instructions & demonstrations. • Testing for & treatment of sexually transmitted infections. • Sterile injecting equipment & drug substitution treatment. • Medical male circumcision. • Post-exposure prophylaxis. • Other novel HIV risk-reduction strategies as they become available. 	<p><i>consistent. However, only EC & GPP require provision of PEP & medical substitution therapy. Only EC requires provision of reproductive healthcare services However, when reading the substantive standard it is clear that all methods should be provided.</i></p>

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		<p>Researchers should guarantee that all communities engaged in biomedical HIV Px trials have state of the art reproductive healthcare services.</p> <p>In GP 16: IC, p. 54: Each prospective participant <i>must</i> be informed... that they will receive counselling concerning how to reduce their risk of HIV exposure & access to risk-reduction means (in particular, male & female condoms, clean injecting equipment, & where relevant, male circumcision)...</p>		
My notes: Within guidelines analysis	<p><i>Outdated given changes in the Px field but does specify that services may be included that are not on the list: "no ltd to".</i></p> <p><i>Does not require provision of PEP even though it states that investigators are morally compelled to provide optimal risk-reduction methods.</i></p> <p><i>Deals mainly with HIV px ("diseases specifically targeted by the vaccine being studies") & not px for "diseases diagnosed as part of the study design" nor "other diseases unrelated to the purpose of the trial" (Tarantola et al., 2007</i></p>	<p><i>Very comprehensive in terms of components although no specific mention made of male circumcision.</i></p> <p><i>Confusing statement that protocols obligate researchers to provide full range of information & services BUT vary in defining the package of services. If all services, then surely package already defined.</i></p> <p><i>Identifying components related to reproductive healthcare & pregnancy Cx seems at odds under SoP → these are more Cx components.</i></p>	<p><i>Very comprehensive.</i></p> <p><i>Deals exclusively with HIV px ("diseases specifically targeted by the vaccine being studies") & not px for "diseases diagnosed as part of the study design" nor "other diseases unrelated to the purpose of the trial" (Tarantola et al., 2007)</i></p>	

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		<i>Focus on HIV px & some mention of “diseases/ (procedures) diagnosed as part of the study” such as pregnancy.</i>		
3. Specific requirements for counselling	<p>Counselling <i>should</i> be: i). Conducted in accordance with recognised <u>national counselling guidelines</u>; ii). Appropriate to participants’ culture, language, gender & age; & iii). Based on <u>reliable information</u> about the prevailing social & behavioural characteristics of the research population (GP 14, RRs, p. 29). -Counsellors <i>should</i> get training, supervision & support (GP 14, RRs, p. 29).</p> <p>The most suitable parties to be risk-reduction counsellors <i>should</i> be considered (GP 14, RRs, p. 28). In order to provide a contribution of lasting benefit to the participating community, consideration <i>could</i> be given to developing the capacity of community members to provide counselling. To prevent any real or perceived conflict of interest, consideration could be given to utilizing counsellors from an independent organisation (GP 14,</p>	<p><i>Counselling:</i> The technique/ frequency/ message content of counselling sessions should be agreed upon by the community-government-investigator-sponsor partnership: based on reliable information about soc-behavioural characteristics (GP 13, SoP, p. 47).</p> <p>Consideration should be given to providing counselling through an agency independent of the investigators. If so, standard must be high. This must be evaluated. Pros & cons must be debated by oversight groups (GP 13, SoP, p. 47).</p>	<p>Risk assessment & risk-reduction counselling— including partner & couple counselling.</p> <p>Trial sponsors, network leadership, & local research teams provide opportunities & time for local stakeholders, in particular community stakeholders, to contribute to trial design issues & procedures such as products to be tested, trial objectives, recruitment strategies, informed consent materials & procedures, reimbursement policies, counselling approaches, follow-up procedures, & post-trial access to trial products or procedures.</p>	

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	<p>RRIs, p. 28).</p> <p>Every effort <i>must</i> be made to ensure that counsellors involved in consent & risk-reduction procedures understand the potentially harmful consequences of participants' mistaken belief that they may be protected from HIV infection (GP 14, RRIs, p. 28) & (GP 9: Potential harms; p. 17)</p>			
My notes: Within guidelines analysis	<i>Cf. DoH (2010) HIV counselling & testing guidelines.</i>	<p><i>Requires agreement amongst the community-government-investigator-sponsor partnership on the technique/ frequency/ message content of counselling sessions. Identified stakeholders do not map with those identified by Tarantola et al (2007) although Tarantola does not specify that all stakeholders must be involved in all decision-making.</i></p> <p><i>It is unclear whether agreement will require mere endorsement of the counselling or negotiated discussions on what the counselling should entail.</i></p>	<i>Only recommendation is the suggestion that RRC involve partners and couples counselling and that local and community stakeholders should make inputs into counselling approaches during protocol development.</i>	
4. Why should Px methods be provided?	Reducing the risk of HIV infection among participants is an essential ethical component of HIV preventive vaccine trials. This is	The principle of beneficence justifies this approach. This obligation pertains not only to the preventive method being studied,	Helping trial participants reduce their risk of acquiring HIV is a key ethical obligation of research teams (Standard of HIV prevention, p. 49).	

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The ethical rationale	<p>especially critical given that phase III efficacy trials rest on some exposure to HIV infection. In order to manage the perceived conflict of interest between risk-reduction & scientific goals of the research, & to promote the welfare of participating individuals, investigators are morally compelled to provide optimal risk-reduction measures to participants. This is clearly captured in <i>Book 1, 3.1.3 x</i>, which states that research objectives are subordinate to the principle that human beings should be treated with respect (GP 14, RRs, p. 28).</p>	<p>but also to reducing the risk that any TP will acquire HIV infection during a biomedical HIV Px trial (GP 13, SoP, p. 45).</p> <p>Some have contended that to promise antiretroviral Rx to HIV Px TPs who become infected would constitute an undue inducement to participate in the trial. That supposition is most unlikely, since biomedical HIV Px trials enrol healthy people, not individuals who are already sick & need Rx. If anything, <i>the possibility of being protected from acquiring HIV by the preventive method itself could conceivably be considered an undue inducement</i>; however, if that were the case, clinical trials of preventive methods could never be ethically carried out. Concerns that any form of Cx & Rx promised to participants in research on biomedical HIV preventive interventions could be an undue inducement are unwarranted.</p> <p>Some may argue that provision of state-of-the-art Px, Cx, & Rx services for participants introduces local inequalities & is therefore unjust when non-participants do not receive those services.</p>		

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		However, all scale-up programmes involve temporary inequalities in the community until universal access can be attained. Achieving a perfect system of equal justice is a long-term process (GP 12, Benefits, p. 44)		
My notes: Within guidelines analysis	No clear rationale – but seems to use compensation for harm argument.	Identify the rationale for providing state of the art Px services as based on beneficence. Tarantola et al. (2007) argue that beneficence & justice both obligate researchers to provide RRs to participants but “these obligations are poorly defined in practical terms, inconsistently understood or inadequately applied.”	Rationale not based on ethical principles but general statement that it is an ethical obligation.	The good governance model states that beneficence & social justice obligate researchers & sponsors to provide services but that these principles are not always easy to apply.
5.1 How should decision be made on what to provide? Role of stakeholder consultation in determining the current package	It is <i>recommended</i> that before the start of a trial, a process of consultation between community representatives, investigators, host government & sponsors be used to design an effective risk-reduction strategy & its parameters (GP 14, RRs, p. 28). Community participation <i>could</i> incl., but not be ltd to, input into appropriate RRs (GP 5, CP, p.10). Community participation should enhance the scientific quality or	Px trials <i>should not be conducted</i> when agreements have not been reached among all research stakeholders on SoP (Context, p. 13). Researchers <i>should engage appropriate stakeholders</i> in tailoring the design, implementation, & oversight of RRs... (GP 13, SoP, p. 46). Participation of the community in the planning & implementation of a biomedical HIV Px product	Determining the components of the HIV prevention package is a joint effort between research teams & relevant stakeholders. Trial sponsors & implementers must work with relevant stakeholders in establishing the type, scope, & process by which participants are provided with, or referred to, services to access the full HIV prevention package. How trial sites help participants prevent HIV acquisition is often at the forefront of community stakeholder concerns. Therefore, successful	<i>All guidelines have a role for stakeholder consultation in making decisions about “what” to provide to participants.</i> <i>MRC, EC & GPP also identify a role for stakeholders in determining “how” RRs should be implemented in the trial.</i> <i>Consultation re implementation is ethically justified. However, consultation may inadvertently serve to lower the substantive standard when the ethical goal is to</i>

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	<p>ethical soundness of the proposed research (GP 5, CP, p.10).</p> <p>The method & process for monitoring RRIIs <i>should</i> be designed & agreed upon by the partnership of community, host, government, investigator & sponsors (GP 15, Monitoring informed consent & RRIIs, p.30).</p>	<p>development strategy can provide at least these favourable consequences: *insight into the design of RRIIs (GP 2: CP, p. 20)</p> <p>The technique, frequency, & message content of counselling sessions should be agreed upon by the community-government-investigator-sponsor partnership, & should be based upon reliable information about the prevailing social & behavioural characteristics of the study population (GP 13, SoP, p. 47).</p> <p>Before a trial commences, researchers, trial sponsors, countries, & communities should agree on a plan for monitoring the initial & continuing adequacy of the informed consent process & RRIIs, including counselling & access to proven HIV risk-reduction methods (GP 17, Monitoring of IC & interventions, p. 56).</p> <p>It is imperative that appropriate financial arrangements are in place to implement agreements made between partners at the time that a study is initiated. These agreements should cover the period of the trial but also address</p>	<p>negotiation with stakeholders about the prevention package to be provided to trial participants is likely to have a significant influence on community stakeholder perceptions of a trial (Standard of HIV prevention, p. 49)</p> <p>Research teams & relevant stakeholders negotiate the HIV prevention package during the protocol development phase of the trial (Standard of HIV prevention, p. 49).</p> <p>Research teams & relevant stakeholders discuss & negotiate the comprehensive HIV prevention package & consult local HIV prevention service providers when appropriate. All scientifically validated methods are discussed, & their appropriateness for the trial design & population assessed (Standard of HIV prevention, p. 50).</p> <p>Research teams & relevant stakeholders discuss & negotiate the comprehensive HIV prevention package, taking account of the following:</p> <p>a. The HIV prevention package required as a minimum for the trial protocol.</p>	<p><i>determine ‘what’ should be provided to participants.</i></p> <p><i>These guidelines only specify the outcome of consultation. They do not specify the process for consultation, the ethical goals of consultation nor any procedures for resolving disagreements. Assumes that all stakeholders will agree, even though identified stakeholders come from vastly different positions in research.</i></p> <p><i>The purpose of consultation varies from agreement, partnership, getting inputs, achieving consensus on various aspects of the SoP.</i></p> <p><i>Only a few stakeholders are identified for involvement in consultation in guidelines.</i></p>

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		<p>what will be provided to study participants once the study is completed (Context, p. 12).</p> <p>Members of the community who may contribute to the development of a safe & effective HIV Px product include....those who provide healthcare & other services to people living with & affected by HIV (GP 2, CP, p. 19).</p>	<p>b. Current HIV prevention standards & services available nationally & locally.</p> <p>c. Current national laws on HIV prevention strategies & services, as well as national ethical guidance on research.</p> <p>d. The trial's funding source, any implications this may have for the prevention package, & how these will be addressed to ensure participants are offered a comprehensive package.</p> <p>e. The HIV prevention services & options that will be offered through referral mechanisms.</p> <p>f. The HIV prevention services that will be available to partners of trial participants.</p> <p>g. The impact that any services offered by the trial, as well as those to which participants will be referred by the trial, could have on local services.</p> <p>(Standard of HIV prevention, p. 51)</p> <p>Research teams & relevant stakeholders discuss how the HIV prevention package will be implemented & monitored, including uptake & standards of referral services (Standard of HIV prevention, p. 51).</p>	

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My notes: Within guidelines analysis	<p>ID's a role for stakeholder consultation in decision-making before & during the research process to design & make inputs into 'appropriate' RRI's & also for monitoring RRI's. Therefore consultation required for 'what' (designing RRI's) & 'how' (monitoring RRI's).</p> <p>Tarantola et al. (2007) provide a comprehensive list of research stakeholders. Not all these stakeholders identified for decision-making in MRC (2003). While Tarantola specifies the process for making decisions, no ethical rationale for consultation is identified nor is there mechanisms for resolving disagreements.</p> <p>While there is concern that consultation may lower the standard that the package be optimal, there is a proviso that community participation should enhance the scientific & ethical conduct of the trial. Therefore the purpose of asking stakeholders what to provide may help to ratchet up the standard of prevention.</p>	<p>ID's a huge role for stakeholder consultation to the 'what' (designing RRI's) & 'how' (implementing & monitoring RRI's).</p> <p>Tarantola et al. (2007) requires consultation on the type, level & duration of px services. In deliberations several criteria are considered including how will uptake of services & implementation be monitored (prospective criteria). Given that an aim of the model is to comply with ethical guidelines it is not clear why stakeholders should deliberate on what to provide as there is a set standard in ethical guidelines.</p>	<p>ID's a large role for stakeholder consultation, discussion and negotiation on 'what' (establishing the type, scope, & process by which participants are provided with, or referred to, services to access the full HIV prevention package) & 'how' (direct provision or referral; implementation and monitoring).</p> <p>Tarantola et al. (2007) requires consultation on the type, level & duration of px services. In considerations several criteria are considered including how will uptake of services & implementation be monitored (prospective criteria)</p> <p>These guidelines map closely with the model to consultation to define the type, scope & duration of prevention available to TPs & host communities.</p> <p>Only guidelines that require consideration of the appropriateness for the trial design & population (Standard of HIV prevention, p. 50).</p>	
5.2. How are	It is recommended that before the start of a trial, a process of	The appropriateness of plans to monitor RRI's should be determined	NIL	UNAIDS EC omits "SoP" as an item in the list for scientific & ethical

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<p>decisions made on what to provide in the current package?</p> <p>Role of research ethics committees (RECs)</p>	<p>consultation between community representatives, investigators, host government & sponsors be used to design an effective risk-reduction strategy & its parameters. The local research ethics committee should approve the risk-reduction strategy (GP 14, RRI, p. 28).</p> <p>The research protocol <i>should</i> outline the benefits that participants in HIV preventive vaccine trials should experience as a result of their participation... At a minimum participants <i>should</i> ...receive comprehensive information regarding HIV transmission & how it can be prevented, & access to appropriate HIV Px methods, including barrier methods...Expected benefits <i>should</i> be described in the research protocol presented to research ethics committees (GP 10: Benefits, p. 19-20).</p> <p>Plans to monitor consent, & RRI, <i>should</i> be submitted for approval to local research ethics committees (GP 15, Monitoring informed consent & RRI, p.30).</p>	<p>by the scientific & ethical review committees that are responsible for providing prior & continuing review of the trial (GP 17, Monitoring of IC & interventions, p. 57).</p> <p>Only anticipated benefits of study-related procedures required for the safe & scientific conduct of the trial should be considered in the risk-benefit analysis, that is, only healthcare benefits derived directly from the study design. Extraneous benefits, such as payment or ancillary services, such as HIV RRI or reproductive healthcare services, should not be considered in the risk-benefit analysis (GP 12, Benefits, p. 43).</p> <p>Consideration should be given to expansion of the responsibilities of the clinical trial monitor to include adherence to ... counselling standards...The appropriateness of such plans should be determined by the scientific & ethical review committees that are responsible for providing prior & continuing review of the trial (GP 17, Monitoring IC & intervention, p. 57).</p>		<p>review! Only monitoring plans need to be reviewed by REC.</p> <p><i>“The ethical review of such protocols normally addresses the issue of what prevention package will continue to be promoted or will be undertaken in order to comply with both ethical standards & the imperative to determine the efficacy & safety of a product against the background of established, ongoing or planned prevention modalities” (Tarantola et al., 2007, p. 4865).</i></p> <p><i>Tarantola et al. (2007) also identify RECs as key research stakeholders to be involved in consultations re the SoP.</i></p>
<i>My notes:</i>	<i>Role for RECs in approving the RR</i>	<i>Role for RECs in approving the</i>		

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<i>Within guidelines analysis</i>	<p>strategy & plans for monitoring the RRs.</p> <p>Consistent with Tarantola et al. (2007) which states that RECs will review the px package. RECs also identified as a stakeholder to be included in consultations.</p>	<p>monitoring plans.</p> <p>Revisions should specify a role for RECs in reviewing & approving prevention services.</p> <p>Not consistent with Tarantola et al (2007) which states that RECs will review the px package. RECs also identified as a stakeholder to be included in consultations.</p>		
<p>5.3.</p> <p>How decisions are made on what to include in the current package?</p> <p>Post-trial access to prevention methods</p>	<p>Risk minimization measures include...Provision of supportive counselling for the duration of the trial, & appropriate referral after the trial is completed (GP 9, Potential harms, p. 18)</p> <p>Capacity of trial-linked healthcare service centres in the host community should be strengthened. That is, the 'local standard of Cx' in the host community should be improved so that it is provided with a contribution of lasting benefit (GP 16, Cx & Rx, p. 33)</p>	<p>Trial sponsors, countries, & researchers <i>should</i> ensure that trials take place only in communities where participants will have access to, & can be referred to, ongoing psycho-social services, including counselling, social support groups, & legal support (GP 11: Potential harms, p. 40).</p> <p>It is imperative that appropriate financial arrangements are in place to implement agreements made between partners at the time that a study is initiated. These agreements should cover the period of the trial but also address what will be provided to study participants once the study is completed (Context, p. 12).</p>	NIL	<p>Tarantola et al. Also have sustainability requirements that must be considered in decision-making (prospective criteria): Sustainability beyond project lifespan: What is the likely sustainability of approaches beyond the end of the research project in technical, operational & financial terms? Who will deliver the services? Who will deliver care & treatment? How? What additional skills & systems would be required?</p>
<i>My notes:</i>	Very vague statement that	Trials should only take place where		

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<i>Within guidelines analysis</i>	<i>counselling services should be available post-trial.</i>	<i>participants can access psychosocial services post-trial.</i>		
<p>5.4.</p> <p>How decisions are made about the current package of prevention?</p> <p>Government & Sponsor Policies</p>	NIL	NIL	<p>Deviations from expected standard HIV prevention packages at a trial site or among trial sites in multisite studies may be caused by national legal restrictions (Standard of HIV prevention, p. 49).</p> <p>When funding-body restrictions limit which prevention methods can be paid for by trial funds, research teams have the responsibility to find other ways to provide these methods, such as through alternative funding streams or linkages with NGOs or CBOs (Standard of HIV prevention, p. 49).</p> <p>Research teams & relevant stakeholders discuss & negotiate the comprehensive HIV prevention package, taking account of the following:</p> <ul style="list-style-type: none"> • Current HIV prevention standards & services available nationally & locally. • Current national laws on HIV prevention strategies & services, as well as national ethical guidance on research. • The trial's funding source, any 	<p><i>Government & sponsors are considered key research stakeholders to be involved in consultations re the SoP.</i></p> <p><i>Further to normative criteria, Tarantola et al require that government & sponsor policies be considered.</i></p>

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			<p>implications this may have for the prevention package, & how these will be addressed to ensure participants are offered a comprehensive package.</p> <ul style="list-style-type: none"> The impact that any services offered by the trial, as well as those to which participants will be referred by the trial, could have on local services. <p>(Standard of HIV prevention, p. 51)</p> <p>Trial sponsors ensure sufficient funding & research teams create a budget & allocate funds & staff time to ensure provision of the comprehensive HIV prevention package (Standard of HIV prevention, p. 51)</p>	
<i>My notes: Within guidelines analysis</i>	<i>No consideration of how sponsor, government policies may factor into decision-making on the SoP, except that counselling should be conducted according to national guidelines. There may be countries where a prevention tool is unavailable & not approved by regulatory authorities → this is not accounted for in these guidelines.</i>	<i>No consideration of how sponsor, government policies may factor into decision-making on the SoP. There may be countries where a prevention tool is unavailable & not approved by regulatory authorities → this is not accounted for in these guidelines.</i>	<i>Sponsor, government & other policies may place restrictions wrt SoP. Stakeholder discussion should consider several factors including government and sponsor policies and/or laws</i>	
6.1. How decisions	As new methods of Px are discovered & validated , these must be added to the preventive	New HIV risk-reduction methods should be added... as they are scientifically validated or as they	Research teams may need to review the HIV prevention package regularly, taking into consideration	<i>Given that Tarantola et al (2007) has not yet been applied to SoP, it does not specify different criteria to</i>

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<p>should be made on adding new methods to the package?</p> <p>Scientific validity & regulatory approval</p>	<p>methods offered to TPs (GP 14, RRs, p. 29, also in bolded GP).</p>	<p>are approved by relevant authorities (GP 13, SoP, p. 45, bolded GP).</p> <p>Mechanisms for negotiation among all research stakeholders, incl. the community, about the standards for enhancement of the risk-reduction package need to be set in the study protocol. Negotiations should take into consideration feasibility, expected impact, & the ability to isolate the efficacy of the biomedical HIV modality being tested (GP 13, SoP, p. 47).</p> <p>A decision to introduce the new method in a trial that is already underway has to be made collectively as it may have implications for resource requirements, sample sizes, & potential futility of continuing the trial (Context: p. 12).</p>	<p>new HIV counselling models & risk-reduction methods that are scientifically validated &, when appropriate, approved by national bodies for use (Standard of HIV prevention, p. 49)</p>	<p><i>consider for evolving standards of prevention. However, issues of scientific criteria & regulatory approval are covered into normative & evaluative criteria.</i></p> <p><i>Jay et al three-step framework may be helpful in terms of clarifying scientific validity and ambiguities regarding regulatory approval.</i></p>
<p>My notes: Within guidelines analysis</p>	<p><i>Scientific validation only – no role for stakeholder consultation.</i></p> <p><i>No direction on how &/or when new methods are scientifically validated – may be defined different by different regulatory authorities (McGrory et al., 2010)</i></p> <p><i>The term “offered” rather than</i></p>	<p><i>Must be scientifically validated or approved by relevant authorities. But what does this mean when normative & regulatory bodies may define these differently (cf McGrory et al., 2010). Also need to consider feasibility, expected impact, & the ability to isolate the efficacy of the biomedical HIV modality being tested.</i></p>	<p><i>Must be scientifically approved, or when appropriate, approved by national regulatory authorities. But what does this mean when normative & regulatory bodies may define these differently (cf McGrory et al., 2010).</i></p> <p><i>These considerations only consider scientific design of the study. Would</i></p>	

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	"provided" is used here.	<p>These considerations only consider scientific design of the study. Would cultural or religious objections be considered? However resources also mentioned in the Context section.</p> <p>Tarantola specifies scientific considerations as part of 1 of 4 criteria of importance in decision-making.</p>	<p>cultural or religious objections be considered? However resources also mentioned in the Context section.</p> <p>Tarantola specifies scientific considerations as part of 1 of 4 criteria of importance in decision-making.</p>	
<p>6.2.</p> <p>How are decisions made on adding new methods?</p> <p>Role of stakeholder consultation</p>	NIL	<p>New methods should be added based on consultation among all research stakeholders (GP 13, SoP, p. 45, bolded GP).</p> <p>Mechanisms for negotiation among all research stakeholders, incl. the community, about the standards for enhancement of the risk-reduction package need to be set in the study protocol (GP 13, SoP, p. 47).</p> <p>The discovery of additional safe & effective biomedical HIV preventive interventions will necessitate discussions among all research stakeholders involved in planned or active trials of other biomedical HIV Px tools. A decision to introduce the new method in a trial that is already underway has to be made</p>	NIL	<p>EC suggests that consultation will play a role and EC holds up a scientific standard too.</p> <p>There is no guidance on how the substantive + procedural standards must work together. What if consultation serves to lower the standard? In fact Macklin (2009) suggests that the procedural standard is a solution to the state of the art requirement in the bolded GP.</p> <p>Adding new methods to the current package will require consultation for the purposes of negotiation, discussion & partnership. In adding new methods, stakeholders are not merely required to agree with the new methods.</p>

Dimension	MRC (2003) HIV Preventive vaccine research. Book 5	UNAIDS (2007). Ethical considerations	UNAIDS-AVAC (2011) Good Participatory Practice (GPP)	My notes: Across guideline analysis
		<p>collectively as it may have implications for resource requirements, sample sizes, & potential futility of continuing the trial. The possibility that such a decision could be required should be anticipated during initial discussions among the research stakeholders (Context: p. 12)</p>		
My notes: Within guidelines analysis	<p>No role for stakeholder consultation when making decisions to add new methods. However, stakeholders may have important inputs to make re feasibility, regulatory & scientific approvals.</p>	<p>Large role for stakeholder consultation ito adding new methods to the package. Again, who constitutes all research stakeholders not defined nor is a process for consultation specified. These guidelines also do not spell out why stakeholders should be consulted → is it respect for communities?</p> <p>Only identifies scientific criteria for not including a method in the standard of prevention. However stakeholders may object to the provision of a prevention method like male circumcision on other grounds such as religious or cultural objections. If circumcision not provided, then consultation would have lowered the substantive standard that the package be state of the art. If circumcision provided despite objections, then stakeholder</p>		

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		<i>consultation is tokenistic & does not appropriately satisfy the principle of respect for communities.</i>		
7. What should be in the protocol?	<p>The protocol <i>must</i> describe potential risks, & steps that will be taken to reduce these risks to minimum...Risk minimization measures that should be taken include: ...ensuring that participants are provided with optimal RRIs(GP 9: Potential harms, p. 18)</p> <p>The research protocol <i>should</i> outline the benefits that participants in HIV preventive vaccine trials should experience as a result of their participation... At a minimum participants <i>should</i> ...receive comprehensive information regarding HIV transmission & how it can be prevented, & access to appropriate HIV Px methods, including barrier methods...Expected benefits should be described in the research protocol presented to research ethics committees, & in the informed consent process (GP 10: Benefits, p. 19-20). The research protocol <i>should</i> specify referral processes for those persons excluded from the trial,</p>	<p>Mechanisms for negotiation among all research stakeholders, including the community, about the standards for enhancement of the risk-reduction package during the trial as new biomedical HIV Px modalities are scientifically validated or are approved by national authorities need to be set in the study protocol (GP 13, SoP, p. 47).</p> <p>Protocols for HIV Px research obligate researchers to provide the full range of information & services for risk-reduction, although they vary in defining the package of services & modes of delivery. If the study aims to test a product by comparing its additive effects to those of routinely practiced Px, in all cases this Px standard should be defined in the study protocol as well as in informed consent documents (GP 13, SoP, p. 45)</p> <p>The research protocol should provide an accurate statement of the anticipated benefit of the procedures & interventions</p>	NIL	<p>According to Tarantola et al. (2007, p. 4865) "in every prevention trial testing a prevention technology (e.g. a vaccine candidate), the standard of prevention offered to trial participants & members of their community is normally set, considering that the very purpose of such trials is to test a technology (in this case a vaccine candidate) against the background of other ongoing or planned prevention activities" & that "standards of prevention form an integral part of the study protocol design".</p>

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
	where relevant (GP4, research protocols & study populations, p. 8).	required for the scientific conduct of the trial. The protocol should outline any services, products, & other ancillary interventions provided in the course of the research that are likely to be beneficial to persons participating in the trials (GP 12: p.43). Research protocols should specify, as fully as reasonably possible, the nature, magnitude, & probability of all potential harms resulting from participation in a biomedical HIV Px trial, as well as the modalities by which to minimise the harms & mitigate or remedy them. (GP 11: p. 40)		
<i>My notes: Within guidelines analysis</i>	<i>Research protocol should outline benefits & risk minimization measures → RRs fall in both. It should also specify referral processes for those excluded from the trial.</i> <i>Consistent with Tarantola et al. (2007) which states that the SoP should be defined in the protocol.</i>	<i>The research protocol should outline: *benefits & risk minimization measures → both which include RR services; *mechanisms for negotiation among all research SHs for adding new tools; *the SoP</i> <i>Consistent with Tarantola et al. (2007) which states that the SoP should be defined in the protocol.</i>	<i>No statement on what should be in the protocol. Only requirement is to allow local and community stakeholders to make inputs into the protocol, including with regard to counselling approaches.</i>	
8. What should be in the informed	Participants must be informed of & should understand the risks & risk minimisation measures that will be	If the study aims to test a product by comparing its additive effects to those of routinely practiced Px, in	NIL Informed consent is a process by	<i>Fairly consistent requirements across the guidelines, except GPP.</i>

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
consent form/ process?	<p>taken, & these measures <i>should</i> be included in the informed consent form (GP 9: Potential harms, p.18)</p> <p>The research protocol should outline the benefits that participants in HIV preventive vaccine trials should experience as a result of their participation... At a minimum participants <i>should</i> ...receive comprehensive information regarding HIV transmission & how it can be prevented, & access to appropriate HIV Px methods, including barrier methods...Expected benefits should be described in... the informed consent process (GP 10: Benefits, p. 19-20).</p> <p>Each prospective participant <i>must</i> be counselled, using appropriate language & techniques, to understand ...that they will receive counselling & access to the means of risk-reduction... (GP 12: Informed consent, p. 22).</p>	<p>all cases this Px standard should be defined in the study protocol as well as in informed consent documents (p. 45).</p> <p>Each prospective participant must be informed... that they will receive counselling concerning how to reduce their risk of HIV exposure & access to risk-reduction means (in particular, male & female condoms, clean injecting equipment, & where relevant, male circumcision)...(GP 16, Informed consent, p. 54).</p>	<p>which a competent individual is provided with enough info about a trial to make an independent decision whether or not to participate in the trial. In this process, research staff members educate the prospective participant about the trial, including about the potential risks & benefits, trial procedures, & what is expected of the participant. When an individual provides consent, this is documented on the informed consent form. Informed consent is an ongoing process. Participants may decide to drop out of the trial at any point, even after providing consent to enrol in the trial (Informed consent, p. 45)</p> <p>To improve relevant stakeholder understanding of the prevention package offered & the clinical trial process, research teams can describe the trial as comparing the study product plus the HIV prevention package, with the placebo (or comparator arm) plus the HIV prevention package (Standard of HIV prevention, p. 49).</p>	<p><i>Info on Px services does not need to be in the IC form per se but must be included in the IC process.</i></p>
My notes: Within guidelines analysis	<p><i>RRIs should be outlined in the IC form (GP 9) & IC process (GP 10). Each TP must be counselled that they will receive RRC & access to</i></p>	<p><i>SoP must be defined in IC documents & each TP must be informed that they will receive RRC & access to RRIs</i></p>		

Dimension	MRC (2003) HIV Preventive vaccine research. Book 5	UNAIDS (2007). Ethical considerations	UNAIDS-AVAC (2011) Good Participatory Practice (GPP)	My notes: Across guideline analysis
	RRIs.			
<p>9.1.</p> <p>How should access to prevention methods be ensured?</p> <p>Mechanisms like research</p>	<p>Counselling should be...Based on reliable information about the prevailing social & behavioural characteristics of the research population (GP 14, RRIs, p. 29).</p> <p>Those who plan & conduct HIV vaccine research should have a good understanding of the social, political, health & cultural context of a specific community or population where the research will occur (p. 9).</p>	<p>Trial sponsors & researchers should collaborate with governments in low- & middle-income countries to explore, develop, & strengthen national & local capacity to deliver the highest possible level of HIV Px, Cx, & Rx services (GP 14, Cx & Rx, p. 49)</p>	<p>Research teams determine which stakeholders already provide HIV prevention services, what types of services they provide, & their capacity to provide adequate services. This will enable research teams to provide optimal referrals & make linkages when necessary (Standard of HIV px, p. 50).</p>	<p><i>EC & GPP require some form of research/ assessment in host communities.</i></p> <p><i>Tarantola et al. (2007) require consideration of both factual criteria (background evidence relevant to decision making such as what prevention services are available in the local community & are there existing referral networks) & prospective criteria (projection of resources, mechanisms, resource needs & impact for each optional approach, e.g., who/how will uptake of services & implementation be monitored). Both require some research or assessment components.</i></p>
My notes: Within guidelines analysis	<p><i>Does not speak directly about Px, apart from counselling, & does not identify the need for research in order to ensure that Px services are accessed during the trial. However, formative research is NB to ID the level of services available in the community in order to establish effective referral networks as well as areas where capacity needs to be built.</i></p>	<p><i>No assessment of the services available in the community/ local healthcare system but does mention the need to explore national & local capacity to deliver Px services.</i></p>	<p><i>Requires an assessment of current providers of HIV prevention services and their capacity.</i></p>	<p><i>There is differential emphasis on the need to do formative research.</i></p>
9.2. How should access to	<p>In order to provide a contribution of lasting benefit to the participating community,</p>	<p>Local capacity may need to be developed to provide RRC in a culturally suitable & sustainable</p>	<p>Research teams & relevant stakeholders discuss & negotiate a stakeholder education plan to</p>	<p><i>All three ethical guidelines consider capacity building mechanisms.</i></p>

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
<p>prevention methods be ensured?</p> <p>Mechanisms like capacity building</p>	<p>consideration <i>could</i> be given to developing the capacity of community members to provide counselling (GP 14, RRI, p. 28).</p> <p>All risk-reduction counsellors should be provided with appropriate training, supervision & support, including ethical responsibilities, lines of accountability &, if necessary, anticipated personal & professional conflicts (GP 14, RRI, p. 28).</p> <p>Sponsors & investigators should build capacity of trial linked healthcare centres to deliver services to the host community, & ensure that there is a contribution of lasting benefit to host communities (GP 16, Cx & Rx, p. 31)</p> <p>Capacity of trial-linked healthcare service centres in the host community should be strengthened. That is, the 'local standard of Cx' in the host community should be improved so that it is provided with a contribution of lasting benefit (GP 16, Cx & Rx, p. 33)</p>	<p>fashion, guided by the best scientific data (GP 13, SoP, p. 47).</p> <p>Researchers should guarantee that all communities engaged in biomedical HIV Px trials have state of the art reproductive healthcare services (GP 13, SoP, p. 45).</p> <p>Trial sponsors & researchers should <i>collaborate</i> with governments in low- & middle-income countries to explore, develop, & strengthen national & local capacity to deliver the highest possible level of HIV Px, Cx, & Rx services through strategic investment & development of trial-related resources (GP 14, Cx & Rx, p. 49).</p> <p>Clinical trials should be integrated into national Px, Rx, & Cx plans so that services provided through clinical trials or arrangements brokered for TPs serve to improve the health conditions of both the TPs & the community from which they are drawn, & (to) support & to strengthen a country's comprehensive response to the epidemic (GP 14, Cx & Rx, p. 49-50).</p>	<p>cover the life-cycle of the trial. The plan defines the following:</p> <p>a. The range of different stakeholders that could benefit from specific education about HIV, HIV prevention options, & general research literacy (GPP for stakeholder education planning, p. 38).</p>	<p><i>"An overall agreement is emerging however among those involved in the conduct of vaccine & clinical trials that it is important to do as much as is feasible to improve medical care to participants in trials as well as to improve care in general in resource-poor settings where trials are conducted"</i> (Tarantola et al., 2007, p. 4863)</p> <p><i>Tarantola et al (2007) also require that the capacity of communities to make decisions is developed.</i></p>
<i>My notes: Within</i>	<i>Capacity building efforts focused mostly on RRC. A general statement</i>	<i>Capacity building to deliver Px services to TPs & to improve health</i>	<i>In terms of the standard of prevention, capacity building is</i>	

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<i>guidelines analysis</i>	<i>in the section on care & treatment on improving capacity of trial-linked healthcare service centres in the community to benefit the host community.</i>	<i>conditions for community</i>	<i>limited to stakeholder education</i>	
<p>9.3.</p> <p>How should access to prevention methods be ensured?</p> <p>Mechanisms like partnership</p>	NIL	<p>Ways <i>should</i> be explored with local authorities to provide trial volunteers & participants with information about HIV Px & Rx services available in the community (GP 13, SoP, p. 46).</p> <p>Trial sponsors & researchers should collaborate with governments in low- & middle-income countries to explore, develop, & strengthen national & local capacity to deliver the highest possible level of HIV Px, Cx, & Rx services through strategic investment & development of trial-related resources. In most situations, no one stakeholder should bear the entire burden of providing resources for such services & the central responsibility for delivery should lie with local health systems (GP 14, Cx & Rx, p. 49)</p> <p>Site selection for moving forward into empirical efficacy trials of biomedical HIV Px technologies is a major challenge. Part of this challenge is the need to integrate</p>	<p>Research teams determine which stakeholders already provide HIV prevention services, what types of services they provide, & their capacity to provide adequate services. This will enable research teams to provide optimal referrals & make linkages when necessary (Standard of HIV prevention, p. 50).</p> <p>Research teams & relevant stakeholders discuss & negotiate the comprehensive HIV prevention package & consult local HIV prevention service providers when appropriate (Standard of HIV prevention, p. 50).</p>	<p><i>Only EC identifies integrating with the local healthcare system as a mechanism of ensuring access to services.</i></p> <p><i>Ito criteria to consider in deliberations, Tarantola et al (2007) require the establishment new collaborative partnerships to provide services (factual criteria)</i></p>

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		<p>biomedical HIV Px tool development with other HIV Px modalities, all of which need to be integrated with HIV Rx & Cx as provided by the local healthcare system. It is imperative that appropriate financial arrangements are in place to implement agreements made between partners at the time a study is initiated. These agreements should cover the period of the trial but also address what will be provided to study participants once the study is completed (Context, p. 12).</p> <p>Site selection for moving forward into empirical efficacy trials of biomedical HIV Px technologies is a major challenge. Part of this challenge is the need to integrate biomedical HIV Px tool development with other HIV Px modalities, all of which need to be integrated with HIV Rx & Cx as provided by the local healthcare system (Context, p. 12).</p> <p>Clinical trials should be integrated into national Px, Rx, & Cx plans so that services provided through clinical trials or arrangements brokered for TPs serve to improve the health conditions of both the</p>		

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
		TPs & the community from which they are drawn, & support & to strengthen a country's comprehensive response to the epidemic. (GP 14, Cx & Rx, p50).		
<i>My notes: Within guidelines analysis</i>	<i>No partnership mechanisms for ensuring access to prevention methods identified.</i>	<p><i>Mechanisms to ensure provision of Px services have been identified – these are located in different GPs across the guidelines – mechanisms should rather be clustered together under the SOP GP.</i></p> <p><i>There should be collaboration with governments to explore, develop, & strengthen national & local capacity to deliver the highest possible level of HIV Px</i></p> <p><i>Suggests that the responsibility to ensure access to services is a shared one with primary lying with the local health systems. There is much emphasis on working with local authorities & government & integration with the healthcare system & national Px plans.</i></p>	<i>Partnerships/linkages with HIV prevention service providers should be developed.</i>	
9.4. How should access to prevention methods be	It is <i>recommended</i> that the following components of risk-reduction be monitored : i) Quality of protocols for counselling, STI management, & referral (GP 15,	Referral mechanisms should be established & follow-up mechanisms instituted to ensure quality case management services (GP 13, SoP, p. 46).	Trial sponsors & implementers must work with relevant stakeholders in establishing the type, scope, & process by which participants	<i>Tarantola et al criteria involve thinking about how each prevention service will be provided.</i>

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<p>ensured?</p> <p>Mechanisms like referral</p>	<p>Monitoring informed consent & RRs, p. 31).</p> <p>Risk minimization measures include...Provision of supportive counselling for the duration of the trial, & appropriate referral after the trial is completed (GP 9, Potential harms, p. 18)</p> <p>The research protocol should specify referral processes for those persons excluded from the trial, where relevant (GP4, Research protocols & study populations, p. 9)</p>	<p>Trial sponsors, countries, & researchers <i>should</i> ensure that trials take place only in communities where participants will have access to, & can be referred to, ongoing psycho-social services, including counselling, social support groups, & legal support (GP 11: Potential harms, p. 40).</p>	<p>are provided with, or referred to, services to access the full HIV prevention package (Standard of HIV prevention, p. 49)</p> <p>Research teams determine which stakeholders already provide HIV prevention services, what types of services they provide, & their capacity to provide adequate services. This will enable research teams to provide optimal referrals & make linkages when necessary (Standard of HIV prevention, p. 50).</p> <p>Research teams & relevant stakeholders discuss & negotiate the comprehensive HIV prevention package & consult local HIV prevention service providers when appropriate (Standard of HIV prevention, p. 50).</p> <p>Research teams & relevant stakeholders discuss & negotiate the comprehensive HIV prevention package, taking account of the following:</p> <ul style="list-style-type: none"> The HIV prevention services & options that will be offered through referral mechanisms. (Standard of HIV prevention, p. 51) <p>Research teams & relevant</p>	

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			stakeholders discuss how the HIV prevention package will be implemented & monitored, including uptake & standards of referral services (Standard of HIV prevention, p. 51).	
<i>My notes: Within guidelines</i>	<i>There is a statement that referrals for risk-reduction services should be monitored as well as a general statement on referral – not linked with ensuring access to Px services & a statement on referral to counselling services post-trial. Mention is made to trial-linked healthcare centres in the GP on care & treatment (see capacity building above).</i>	<i>There is a statement that referral mechanisms should be established & monitored.</i>	<i>Explicit statements the HIV prevention options may be provided via referrals and that standards of referral services should be monitored.</i>	
9.5. How should access to prevention methods be ensured? Mechanisms like advocacy	Strategies to offset vulnerability include capacity building for, & the early involvement of, participating communities (see Point 5), the development of advocacy processes & meaningful & ongoing informed consent procedures (see Points 12 & 13). Factors of particular reference to HIV vaccine research (see Point 13) include: Legal marginalisation of groups from which participants might be drawn, such as ... intravenous drug users ...& limited availability & sustainability	Trial sponsors, researchers & advocates should continue efforts to resolve conflicts about legal constraints on public health practice such as abortion or interventions for IDUs (GP 13, SoP, p. 46).	<i>NIL</i>	<i>Only EC specifically identifies a role for advocacy in ensuring access to Px services, particularly those considered illegal in some contexts, e.g., provision of clean needles.</i> <i>MRC & GPP provide no guidance on what to do in contexts where Px services are considered illegal.</i>

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	of healthcare & Rx options (GP 7, vulnerability, p. 15)			
<i>My notes: Within guidelines analysis</i>	<p><i>MRC does not directly address advocacy as a mechanism in ensuring Px services. The closure of PrEP trial provides NB evidence of the role of advocacy in trials as well as the consequences of failure to provide an OPTIMAL package regardless of legality</i></p> <p><i>However in the GP on vulnerability it mentions that advocates could play a role in addressing the needs of legally marginalised communities like IDUs.</i></p>	<i>EC identifies that when there are legal constraints in providing components of the package, efforts should be made to resolve such conflicts. It does not address the role of advocacy in improving the local SoP.</i>		
10. What should be monitored?	<p>A plan for... evaluating the quality of RRIs, should be agreed upon before the trial commences & be implemented throughout the trial (bolded GP: 15, Monitoring informed consent & RRI's, p. 30).</p> <p>RRIs should be evaluated to ensure that quality interventions are provided to participants throughout the trial (GP 15, Monitoring informed consent & RRI's, p. 30)</p> <p>It is <i>recommended</i> that the following components of risk-reduction be monitored: i) Quality</p>	<p>Before a trial commences, researchers, trial sponsors, countries, & communities should agree on a plan for monitoring the initial & continuing adequacy of the informed consent process & RRIs, including counselling & access to proven HIV risk-reduction methods (GP 17, Monitoring IC & interventions, p. 56, bolded GP).</p> <p>The provision of HIV RRC should be monitored to ensure quality & to minimise the potential conflict of interest between risk-reduction goals & the biomedical Px trial's</p>	Research teams & relevant stakeholders discuss how the HIV prevention package will be implemented & monitored , including uptake & standards of referral services (Standard of HIV prevention, p. 51).	<i>Ito monitoring Tarantola et al (2007) specify that monitoring & accountability are important considerations in decision-making, that is, who should make sure that the proposed standard is actually being implemented? How will the approaches be monitored? What should be the transparency & mutual accountability obligations?</i>

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	<p>of protocols for counselling, STI management, & referral; ii) Cultural, linguistic, gender & age appropriateness of the counselling for target groups; iii) Counsellor skills & the degree to which counsellor training corresponds with policy developed by the National Minimum Standards Committee for the Accreditation & Training of HIV/AIDS counsellors; iv) Procedures by which risk-reduction counsellors are selected, trained & supervised; v). Availability of adequate supplies of barrier methods & risk-reduction materials; & vi) RRIs should also be evaluated by participant satisfaction, & with regard to their efficacy in reducing high-risk behaviour (GP 15, Monitoring informed consent & RRIs, p. 31).</p> <p>To reduce a real or perceived conflict of interest, evaluation of risk-reduction measures <i>could</i> be done by, or in collaboration with, an independent agency. (GP 15, Monitoring informed consent & RRIs, p. 31).</p> <p><i>Consider</i> appointing an independent monitor, or expanding the trial monitor's</p>	<p>scientific goals (GP 13, SoP, p. 47).</p> <p>National & international research oversight groups should evaluate the pros & cons of independent organisations implementing RRIs in biomedical HIV Px trials; where such efforts are warranted & feasible, they should be undertaken & rigorously evaluated (GP 13, SoP, p. 47).</p> <p>Monitoring should include quality assurance of gender- & culture-sensitive counselling services, appropriate procedures for adolescents, & evaluation of the impact of the trial on the vulnerabilities of the communities involved in the study (GP 17:, p. 56)</p> <p>Consideration should be given to expansion of the responsibilities of the clinical trial monitor to include adherence to the recruitment & informed consent processes & to counselling standards (GP 17, Cx & Rx, p. 57).</p> <p>Ways <i>should</i> be explored with local authorities to provide trial volunteers & participants with information about HIV Px & Rx services available in the</p>		

<i>Dimension</i>	<i>MRC (2003) HIV Preventive vaccine research. Book 5</i>	<i>UNAIDS (2007). Ethical considerations</i>	<i>UNAIDS-AVAC (2011) Good Participatory Practice (GPP)</i>	<i>My notes: Across guideline analysis</i>
	responsibilities, to evaluate risk-reduction measures (GP 15, Monitoring informed consent & RRs, p. 31).	community. Referral mechanisms should be established & follow-up mechanisms instituted to ensure quality case management services (GP 13, SoP, p. 46).		
<i>My notes: Within guidelines analysis</i>	<i>RRIs should be monitored for quality as well as monitoring of referral. Most of the emphasis is on RRC but some mention of other strategies.</i>	<i>RRIs should be monitored, particularly the provision of RRC, as well as referral mechanisms.</i>	<i>Uptake of Px services should be monitored as well as adequacy of referral networks but no mention of monitoring RRs for quality.</i>	<i>Tarantola et al provides a process for documenting all decisions about the standard of prevention. This is an important requirement given the emphasis on consultation in the guidelines.</i>
11. What should be documented?	NIL	NIL	Research teams maintain clear written records of discussions & agreements. This includes recommendations, actions taken by the research team, & any unresolved issues that require follow-up (Standard of HIV prevention, p. 51).	
<i>My notes: Within guidelines analysis</i>	<i>NIL. NB considering emphasis on SH consultation in decision-making. However, assumption that any monitoring will require documentation as well.</i>	<i>NIL. NB considering emphasis on SH consultation in decision-making.</i>	<i>All discussion and agreements should be documented..</i>	<i>A key outcome of the GGM is to document terms of agreement & responsibilities prior to the trial (Tarantola et al., 2007)</i>

Appendix 2: Letter to Principal Investigators



Trial site PI
HIV vaccine trial site name
Organization
Address
Phone/ Email

Dear (Principal Investigator),

Thank you for attending our consultation on 1st July 2009, or sending a site representative. As mentioned at the consultation, and in our circulated report, HAVEG has been funded by a grant from the Wellcome Trust to explore **care and prevention responsibilities** in HIV vaccine trials.

Our study aims to explore trial participants' access to care and prevention **services** such as treatment/care for HIV (and other conditions identified in trials), as well as counselling, condoms, circumcision, PrEP and treatment for Sexually Transmitted Infections. It also aims to explore **decision-making** to provide such services. Our ultimate goal is to explore whether current ethical guidelines correspond with on-the-ground practices and anticipate actual stakeholder challenges. The study is conducted in the spirit of shared struggle towards a mutual goal of an effective prevention technology for all.

Our research methods will be (1) document review (2) interviews and (3) questionnaire administration.

With this letter, **we are requesting access to site documents** that could shed light on care and prevention practices at your site.

All the information you provide will be subject to the following protections:

- Neither you nor any member of your staff will be named in any public report
- Your site will not be named in any public report
- Before release of final public reports, practices at individual sites will be aggregated into a national picture
- Before release of final public reports, our results will be presented at a consultation where comments and inputs from sites will be solicited

HIV AIDS VACCINES ETHICS GROUP

School of Psychology University of KwaZulu-Natal

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- Only designated members of the team who have signed strict confidentiality agreements will review the documents and they will not be released or accessed by any third parties
- Trial sponsors have been advised about this project and have expressed their general support (the [REDACTED])
- The study has been approved by the following Research Ethics Committees (insert approval numbers):
 - ✓ BREC at University of KwaZulu-Natal: BE 241/09
 - ✓ Wits HREC (Medical: M091140 (R14/49)
 - ✓ MEDUNSA: MREC/P/13/2010: CR
 - ✓ University of Cape Town HREC: REF 476/2009
 - ✓ Walter Sisulu: (under review)

Please note that you are of course free to refuse to release documents to us. If we can review documents in advance, this may reduce time needed for interviews. If you do release documents, this does not necessarily mean you will approve of interviews being conducted at your site or that you will agree to such interviews yourself. We may need to contact you to help us make sense of some of the documents.

If you agree to release documents to us, the following may be helpful to our study:

- ✓ Ethics applications and protocols for HIV vaccine trials [REDACTED]
- ✓ Feedback from research ethics committees
- ✓ Site/protocol specific documents regarding **care** for conditions identified in trials (such as HIV, TB, hypertension etc)
- ✓ Site/protocol specific documents regarding **prevention** practices (counselling, condoms, PEP, male circumcision, STI treatment)
- ✓ Standard operating procedures (SOPs)
- ✓ Memorandum of Agreement with referral centres
- ✓ Manual of operations
- ✓ Training materials
- ✓ Any others?

There may be other relevant documents that we have not listed above and we would be grateful for any information that, in your view, might clarify care and prevention practices at sites.

We appreciate your time and support of this project.

Yours sincerely,

Graham Lindegger (PI)

Cathy Slack Co-PI

Appendix 3: Introductory presentation to individual sites

**Researching prevention & care in
HIV vaccine trials in South Africa**

HIV AIDS VACCINES ETHICS GROUP
<http://www.saaavi.org.za/havesg.htm>

9th July 2010





Who are we?

- HIV AIDS Vaccines Ethics Group
- Based at UKZN School of Psychology (PMB)
- PI: Graham Lindegger; Co-PI: Cathy Slack; researchers Zaynab Essack, Jen Koen
- Multi-disciplinary team (collaborators & consultants & interns)
- Funded by SAAVI 2000-2009; Wellcome Trust 2009-2012.
- Do ethical-legal research and resource development
 - ✓ Informed consent
 - ✓ Children (e.g. Part of SASHA consortium)
 - ✓ Standard of prevention and care
- See <http://www.saaavi.org.za/havesg.htm>

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What is the purpose of this meeting?

- To describe our proposed research into care & prevention
- To hear inputs/ concerns
- To establish if there is interest in taking part in our study
- If so, to plan the most optimal approach for implementation at a later meeting
- (this is not an ethics talk on care/prevention nor a data collection visit)

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Where are we in the research process?

- We have got funding for research exploring care & prevention (April 2009)
- We have appraised trial funders of the proposed research (May 2009)
- We have held a consultation with site staff & CAB reps from all sites to hear concerns & incorporate into protocol (July 2009)
- We developed a research protocol exploring care and prevention & have ethical clearance (Aug 2009 – March 2010)
- We have examined ethical guidelines about care & prevention
- We have reviewed "master protocols" for phase IIB and phase I trial
- We are starting site visits to explore if sites wish to be involved & if so how
- We have NOT collected empirical data from sites

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What is the issue?

- There has been debate about:
 - ✓ The responsibilities of HIV vaccine trial researchers to ensure that participants don't get HIV and to address the care needs of trial participants including HIV
 - ✓ The role of CABs and RECs in ensuring that responsibilities to participants are met.
- There is also ethical guidance on care & prevention (SANAS, 2004; LINDEGGER, 2005; GIP, 2005; OPTIMA, 2006)
- There has been no detailed exploration with researchers, CABs, and RECs about:
 - ✓ The steps they take
 - ✓ The challenges they face
 - ✓ The successes they are having, and
 - ✓ Their views of the ethical resources

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What are the aims of this project?

- To understand what ethical guidelines expect of stakeholders
- To explore with sponsors, researchers, CABs, and RECs the steps they take in relation to prevention & care, challenges & successes & views of the ethical guidelines
- To assess if current ethical guidelines respond to the dilemmas of stakeholders and if steps taken resonate with what ethical guidelines expect
- To recommend changes to ethical guidelines and stakeholder practices, where necessary

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What might the research involve for stakeholders?

- Answering a brief **questionnaire** on views of ethical standards
- Being part of an **interview** about prevention/ care
- Allowing access to **documents** or materials that address prevention/ care
 - (e.g. Training materials, SOPs etc)

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What are the risks & protections?

- For the brief **questionnaire** on ethical guidelines, people may worry we are testing their knowledge of ethical guidelines & that sites/site structures will be identified in a public report
- ✓ We are more interested in what our volunteers think of ethical guidelines & we will not analyse questionnaires per site: rather we will pool it & look at views across stakeholder group
- E.g. We will NOT say things like "The [name of site] CAB thinks that informed consent requirements are a strong ethical protection"
- We WILL be able to say things like "CAB representatives at sites view community consultation as a strong protection".

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What are the risks & protections?

- For the **interviews**, participants may worry that there may be negative consequences for sites if they talk about problems & that sites will be identified in a public report
- ✧ Only in the exceptional and unlikely event of a serious breach of practice that threatens participant welfare will steps be taken. People can refuse to answer certain questions or make disclosures. No site details will be released in public reports. We will pool data to get a picture of stakeholder practices, challenges, and perspectives
- E.g. We will NOT say things like "At the [name of site], site staff say that they worry most about the quality of care received at referral sites".
- We WILL be able to say things like "Site staff generally reported that managing referrals is very demanding".

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Cont'd

- Anonymised data
- National consultation
- REC approval
- Gate-keeper permission (site PI, CB chair)
- Individual informed consent
- Opt-out of certain questions or withdraw at any point
- No direct observation of any prevention/ care procedure (on-site or referral)
- No data collection from trial participants
- National consultation for draft results prior to release of public report

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What would be the possible benefits if any?

- We will have a better understanding of what ethical guidelines expect of stakeholders
- We are likely to have a good understanding of whether stakeholders think ethical standards can be understood, implemented and protect participants. This will help us make recommendations to revise guidelines.
- We are likely to have a good understanding of the steps various stakeholder groups undertake to address participants prevention and care needs, and what is working well or poorly. This will help us make recommendations to amend practices where necessary.
- We will be able to give individual trial sites/ site structures feedback on what we found if they would like that.

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How would we disseminate results?

- Feedback to individual sites/ site structures, if desired
- National consultation to discuss results
- Summary of results to participants
- Public report
- Manuscripts

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What have we done so far at [name of site]?

- Telcon with PI & site director to plan today's talk
- Letter to HR advising them of today's talk
- Copy of ethical approval to site
- There is lots of planning still to do

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Thank you

- Thank you for your time and attention

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Appendix 4: Information sheet and informed consent form

Information Sheet: Care and prevention in HIV vaccine trials in South Africa: A normative and empirical exploration

Dear Colleague,

Hello. We are from the HIV/AIDS Vaccines Ethics Group (HAVEG), based at the University of KwaZulu-Natal. HAVEG does ethical-legal research in HIV vaccine trials.

We are inviting you to participate in a study.

This study will explore care and prevention in HIV vaccine trials.

Who funds our study?

This study is funded by the Wellcome Trust, a UK-based charity that funds health research.

What is the purpose of our study?

Our study will look at how researchers help HIV vaccine trial participants to avoid HIV, get care for HIV if they do get infected, or get care for other health problems. It will look at how these important decisions are made. In other words, we are exploring care and prevention **practices** at HIV vaccine sites in South Africa ó delivery of services to participants and decision-making to provide services.

We are interested in the challenges and successes experienced by researchers, as well as the concerns and views of other stakeholders on this issue (e.g. members of Community Advisory Boards (CAB), ethics bodies and sponsor teams).

We are also interested in the views of stakeholders about **ethical standards** in recent guidelines on HIV vaccine trials.

We want to see whether what happens in practice matches what ethical guidelines say should happen. If there is not a good match, we want to understand why: for example, are ethical guidelines too difficult to implement? We also want to see if ethical guidelines help stakeholders with the actual concerns and worries they have. If guidelines don't address people's real concerns, how can they be improved?

Based on the findings, we will make recommendations to strengthen care and prevention practices (including the sharing of best practices), and to make ethical guidelines clearer or stronger.

What inputs have sites and community representatives had into our study?

In July 2009, we met with site staff and CABs from all HIV vaccine trial sites to tell them our broad aims and get their views and concerns. We clarified that the research was part of a collaborative effort towards a shared goal of strong care and prevention at South African sites. There seemed to be general support for the study.

What procedures will this study involve?

We will conduct general interviews with some site-staff (e.g. PIs, medical officers) and some other stakeholders (e.g. CAB members, review body members, sponsors). The interviews will explore their views about the important issues in care and prevention in HIV vaccine trials, and challenges and successes. For selected site staff, we will also conduct a detailed specific interview about what is actually provided to participants at their sites and how.

We will also ask site staff and members of CABs and RECs to answer a questionnaire that explores their views of ethical guidelines for HIV vaccine trials.

Later on we may ask some stakeholders to be involved in focus groups.

As background to gathering data from people, we will also be looking at various documents. We will look at ethical guidelines to understand what is expected of researchers. Where we get permission, we will also look at documents like HIV vaccine trial protocols, standard operating procedures and training materials. We will also try to understand each site better by looking at information on their websites or public documents.

Why have you been chosen?

You have been identified as someone we would like to talk to because of your work at HIV vaccine sites or your involvement in a community organisation, review body or sponsor team.

Do you have to take part?

No. You can refuse to take part. Even if you agree, you can change your mind at any time. You can also refuse to take part in certain procedures or answer certain questions. You can also choose to make your answers hypothetical and not about the actual group or institution you represent.

What are the risks of taking part in this study?

If you are taking part in an interview, you may feel worried to talk about care and prevention practices that are not working well in the group or institution that you are a part of. You may worry that talking about these will have negative consequences for you or your organisation. Remember that you can choose not to take part, or not to answer certain questions. You can also make your answers general and not about your actual organisation.

We will make every effort to make your responses anonymous. We will not report any names of people when writing reports. We will group together information about sites into a national 'picture' before any public release. This information will be shared with stakeholders at a national consultation before public dissemination.

We are not tasked to monitor practices. However, if you inform us of something that appears to be a serious breach of practice that poses a direct risk to the health and welfare of an actual HIV vaccine trial participant, then it seems wrong for us to do nothing. So in this event, we will discuss the issue in a confidential research meeting. We may ask you for more details. A decision may be made to contact the site Principal Investigator for clarification and remedial action if necessary. In this event you will be informed and every effort will be made to maintain your confidentiality and resolve the issue in a collegial and respectful manner. Sites may have to contact their research ethics committee and/or other institutional bodies as per their own arrangements.

If you are taking part in the questionnaire, you may worry that we are testing how much you know about ethical standards. This is not the case: rather, we hope to identify those areas where ethical standards may have to be clarified, disseminated better, or even changed.

What are the benefits of this study?

There are no direct benefits to participants. It is possible that taking part in the study makes you think about the issues in a new and more helpful way, however there is no guarantee that this will happen.

In the long run, we hope this research will identify (at a national level) practice areas that need strengthening as well as best practices. We also hope that recommendations for improved guidelines will make for clearer direction on this issue.

A site-level report identifying issues, challenges and successes at each site will be offered to participating sites to maximize benefits to them.

What will happen to the data and how will confidentiality be maintained?

In general, only research staff at HAVEG will have access to the data from this study.

If you take part in interviews, your name and other identifying details will not be stored together with any data. We hope to record your interview using a digital recorder. This recording is only for our own records, so that we can get an accurate record of what is said. We will transcribe parts of the recording.. You may refuse to be recorded if you wish.

Because there are a small number of target groups, it is possible that interviewees will be identifiable through, for example, rich text quotes. Every effort will be made to make interviewees as anonymous as possible.

If you take part in the questionnaire, your name and other identifying details will not be stored together with any data.

If you take part in focus groups held later on, you will be asked not to disclose things that are discussed in the group. We can't guarantee that every focus group participant will honour this agreement, so we will ask all focus group participants to be careful about disclosing information. Focus groups may be recorded if participants agree.

The tape recordings, transcripts and questionnaire data will be stored safely, that is, in a locked cabinet, and electronic records will be password protected.

All the data will be kept for 5 years then destroyed.

What will happen to the results?

Results will be written into:

- A national report for discussion at a national consultation and eventual public dissemination
- Academic publications in open access journals
- Conference presentations
- Two doctoral dissertations, if post-graduate approval is received.

No participants in our study will be named in any written document and efforts will be made to prevent their personal identification. Also, every effort will also be made to avoid the

identification of specific sites. Sites will not be named in written reports. Site data will be aggregated to form a national picture. However, due to the fact that there are only limited HIV vaccine trial sites in South Africa, it is conceivable that some sites may be identified.

A national-level report will be developed and discussed at a national consultation. An individual report tailored to each site will be offered to each site, but not for public release.

What do you need to do?

If you agree to participate in this study, we will need you to sign the informed consent form below and return it to us. We will ask you to discuss any questions you may have about the study with us.

If you are a member of a trial site, CAB, review body or sponsor team taking part in a general interview about concerns and challenges, we will need about 1 to 2 hours of time. This may be in person or over the phone.

If you are member of a trial site taking part in a specific interview about care and prevention practices we will need about 1 to 2 hours of time. This may be in person or over the telephone.

If you are a member of a trial site, CAB or REC taking part in a questionnaire about ethical standards, we will need about 30 minutes. This may be in person, over the telephone or over email.

At a later stage you may be asked to participate in a follow up focus group.

Remember, even if you agree to take part in some procedures you can refuse to participate in others.

NOTE: You may not be invited to take part in all of these procedures, because some are reserved for particular stakeholder groups.

Will participants in this study be paid?

Site staff and members of CABs, review bodies and sponsor teams taking part in a *general semi-structured interview* will be offered R50.00 as payment to compensate them for their time, inconvenience and expenses.

Site staff taking part in *specific interviews about care or prevention practices* will be offered R50.00 respectively.

Site staff, CAB members or REC members who take part in a *questionnaire about ethical standards* will be offered R35.00.

If we hold *focus groups* later on, participants will be offered R50.00.

NOTE: You may not be asked to take part in all of these instruments, because some of the instruments are reserved for particular stakeholder groups.

Was this research ethically approved?

Yes. This study has been approved by the following ethics committees:

- | | |
|---------------------------------------|--------------------|
| ➤ BREC at University of KwaZulu-Natal | BE 241/09 |
| ➤ Wits HREC (Medical) | M091140 |
| ➤ MEDUNSA | MREC/P/13/2010: CR |
| ➤ University of Cape Town HREC | REF 476/2009 |
| ➤ Walter Sisulu | 089/009 |

Who can I contact if I have questions?

For questions related to the study, please contact the PI who is Graham Lindegger at 033 260 6166 or lindegger@ukzn.ac.za. You may also contact the co-PI who is Catherine Slack on 033 2606166 or slackca@ukzn.ac.za

For questions about ethical issues in the study, you may contact the BREC ethics committee through Ms A Marimuthu on 031 260 4769, fax 031 260 4609 or email brec@ukzn.ac.za

For Cape Town based participants: For questions about ethical issues in the study, you may contact the UCT HREC through Ms Lamees Emjedi on 021 406 6338 or email Lamees.Emjedi@uct.ac.za

DECLARATION

Consent to take part

I, _____ (full names of participant) confirm that I understand this consent form and the nature of the study and agree to take part in:

	Insert X
The general interview on care / prevention	
The specific interview on care / prevention (Site staff only)	X
The questionnaire on ethical guidelines related to care and prevention	
The focus group	

I understand that I can withdraw from the study/ components of the study at any time.

SIGNATURE OF PARTICIPANT

DATE

Tape recording consent

I, _____ (full names of participant) consent to the tape-recording of the interview or focus group.

SIGNATURE OF PARTICIPANT

DATE

Appendix 5: Semi-structured interview guide for the prevention-specific interview

NOTE: These were the kinds of questions asked. However, the guide was adapted and refined as data collection proceeded and for each stakeholder group, where relevant.

Interviewer to explore current prevention service, e.g.

- What prevention services do participants receive?
 - Risk-reduction counselling
 - Male and female condoms
 - STI diagnosis and treatment
 - Male circumcision
 - PEP
 - Other? E.g. Clean needles

Interviewer to explore EACH of the tools identified by interviewee (above), e.g.

- Who receives these services (e.g. TPs only, screen-outs, partners, the community)?
- How are prevention services provided (direct provision or referral)?
- To what extent is referral assisted or formalised?

Interviewer to explore decision-making practices and perspectives, e.g.

- How is it decided which methods to provide or not?
- Which stakeholders groups are involved in decision making? Can you describe the nature of their involvement?
- Have there ever been disagreements among stakeholders on what to include in the risk-reduction package? If so, how have these been resolved?
- Have you found ethical guidelines helpful in making decisions about what prevention services to provide to participants?
- Ethical guidelines require that participants should be provided with state of the art, optimal or proven HIV prevention methods. What do you think about these requirements?
- How are decisions made on who pays for prevention services to be provided to participants

Prompts to explore: proven efficacy; acceptability, resources; sponsor policy, ethical guidelines, community input, ethics input, characteristics of population; sustainability

Interviewer to explore issues of adding new prevention methods, e.g.

- What is the process for adding new methods to the risk-reduction package?
- Reflecting on the issue of circumcision, can you describe key considerations in adding new methods?
- Anticipating the results of PrEP and microbicides, can you describe key issues in adding new methods?
- What are your thoughts on new ethical guideline requirements that new prevention methods should be added based on consultation among all research stakeholders when they are approved or scientifically validated? Is this feasible?

Interviewer to consider asking more general questions, e.g.

- Are services **monitored** for (i) uptake and (ii) quality?
- How, if at all, does the trial help to **build capacity** in the local health care system?

- Is **feedback** given to stakeholders on the prevention services that participants get?
- You mentioned X was critical, can you tell me more about that?
- Have there ever been disagreements among stakeholders on what to include in the risk-reduction package? If so, how have these been resolved?
- **Why** do you think participants should be provided with prevention services?

Appendix 6: Semi-structured interview guide for the general interview on care and prevention

NOTE: These were the kinds of questions asked. However, the guide was adapted and refined as data collection proceeded and for each stakeholder group, where relevant.

A Interviewer to ask general questions on interviewee role in trials, e.g.

- What has your role been in HIV vaccine trials generally?
- What is your role/involvement in relation to care and prevention in trials?

B Interviewer to explore general issues, e.g.

- From your perspective what are the key issues in care and prevention in HVTs?
- What challenges do you face about this issue, and how have you addressed them?
- In your view, what has worked well/badly?

C Interviewer to explore issues around decision-making, e.g.

- When reflecting on how decisions get made to provide services, what comes to mind?
- How are decisions made about what services to provide?
- To what extent have (or should) key stakeholders been involved?
- Can you describe successes or challenges?

D Interviewer to explore factors influencing practices, e.g.

- Can you describe access to care and prevention services in the general community?

E Interviewer to explore ethical guidance, e.g.

- In general, what are your overall impressions of the ethical guidance on this issue?
- What are some of the big issues we should understand about the ethical guidance?
- How well do you think guidelines help you with your dilemmas about this issue?
- What do you think some of the challenges are in implementing ethical guidance?
- Do you think that guidelines are helpful for making decisions around practice on the ground?
- Why do you think participants should be provided with care and/or prevention services?

F Interviewer to explore interviewee-prioritized issues & themes, e.g.

- You mentioned X was important, can you tell us more about that?

Appendix 7: Transcript conventions

- An identifier was allocated to each respondent to ensure anonymity (e.g., Z16, REC), to indicate that this was the 16th interview conducted by the researcher, with an REC member).
- Each speaker was clearly identified throughout the transcript (R=researcher; V=volunteer).
- Some details of the conversation other than words were included, for example laughter and sighs.

Specific conventions are detailed below:

(interruption)	interruptions of the interviews were recorded
(.)	a period in parenthesis indicates a short pause
(pause)	Indicates a long pause
_____	Underlining indicates particular emphasis or stress on a particular word
(unclear)	indicates inaudible bits of speech
((words))	words in double parentheses indicate that the transcriber is guessing at what is being said, because speech is unclear – transcriber is not certain that this is exactly what is being said.
/	A sudden change in the direction of talk was indicated by a forward slash, e.g. Standards of prevention are/at this site we provided condoms to all participants

Appendix 8: Coding framework

A. DECISION MAKING PRACTICES AND PERSPECTIVES ON THE STANDARD OF PREVENTION

1. Stakeholders involved in decision-making
 - 1.1. Protocol writing team
 - 1.1.1. Sponsor representatives
 - 1.1.2. Network representatives
 - 1.1.3. Local investigators/site staff
 - 1.1.4. Local CAB
 - 1.2. Local trial sites
 - 1.3. REC involvement
 - 1.4. MCC
 - 1.5. SA government/DOH involvement
 - 1.6. Trial participants
2. Protocol writing practices
3. Relevant criteria for designing the standard of prevention package
 - 3.1. Affordability (cost of the intervention)
 - 3.2. Availability of funding
 - 3.3. Available in host country (local standard of prevention)
 - 3.4. Clear information (clear counselling messages)
 - 3.5. Effects of combining prevention modalities
 - 3.6. Ethics requirements
 - 3.7. Impact on trial feasibility
 - 3.8. Investigator requests/demands
 - 3.9. Level of evidence
 - 3.10. Participant requests
 - 3.11. Phase of the trial/Risk-level of participants
 - 3.12. Preventing undue inducement
 - 3.13. Regulatory approval
 - 3.14. Required statistical power
 - 3.15. Responding to site-specific/protocol specific/case specific demands
 - 3.16. Scientific validity
 - 3.17. Sponsor policy
 - 3.18. Sustainability post-trial
 - 3.19. To retain participants
 - 3.20. Type of population
4. Rationale for providing (not providing) a standard of prevention
 - 4.1. A fair thing to do
 - 4.2. An ethical obligation
 - 4.3. Beneficence
 - 4.4. Duty of rescue
 - 4.5. Morally praiseworthy
 - 4.6. Non-maleficence
 - 4.7. Prevention is better than treatment
 - 4.8. Reciprocal justice

- 4.9. Satisfying ethical guidelines and requirements
 - 4.10. The right thing to do
 - 4.11. To counteract behavioural disinhibition
 - 4.12. To facilitate informed decision-making
 - 4.13. To help participants remain negative
 - 4.14. To reduce misperceptions that trials increase HIV
5. Decision-making process
- 5.1. Consulting CABs
 - 5.2. Consulting ethics groups
 - 5.3. Consulting investigators
 - 5.4. Face-to-face meetings (protocol-writing practices)
 - 5.5. Informal dialogue
 - 5.6. Protocol-by-protocol
 - 5.7. Scientific discussions
 - 5.8. Site-by-site
 - 5.9. Small groups to resolve specific issues
 - 5.10. Standardised package
 - 5.11. Through protocol review
 - 5.11.1. Protocol as a mechanism of consensus
6. Stakeholder decision-making roles and practices
- 6.1. Protocol writing team
 - 6.1.1. Developing (drafting) protocol
 - 6.1.2. Discussing standard of prevention
 - 6.2. Sponsor representatives
 - 6.2.1. Sponsor as dictator
 - 6.2.2. Sponsor dominates numbers
 - 6.2.3. Sponsor as meeting leader
 - 6.2.4. Funding
 - 6.3. Network representatives
 - 6.3.1. Finding funding
 - 6.3.2. Overseeing trial implementation
 - 6.4. Local investigators/site staff
 - 6.4.1. Investigator as driver of decision-making
 - 6.4.2. Investigator as advocate
 - 6.4.3. Site staff decide on what to offer participants on individual need basis
 - 6.5. Local CAB
 - 6.5.1. CAB input (or lack thereof) in making decisions
 - 6.5.2. Rationale
 - 6.5.3. Benefits
 - 6.5.4. Challenges
 - 6.6. Local sites
 - 6.6.1. Site-level decisions on what to provide
 - 6.7. REC involvement
 - 6.7.1. Approving deviations from the protocol
 - 6.7.2. Approving the standard of prevention
 - 6.7.3. No input/advocacy on standards of prevention
 - 6.7.4. Protecting participants
 - 6.7.5. REC capacity

- 6.7.5.1. Community representation on REC
 - 6.7.6. REC requirements for the standard of prevention (including implementation)
 - 6.7.7. Reviewing the protocol
 - 6.8. MCC
 - 6.8.1. Reviewing the protocol
 - 6.9. SA government/DOH involvement
 - 6.9.1. Referral centre
 - 6.9.2. Procurement source
 - 6.10. Participants
 - 6.10.1. Decide which services to take up
 - 6.11. Stakeholder relationships
7. The evolving standard of prevention (adding new tools)
- 7.1. Participants substitute new interventions for old ones
8. Decision-making challenges
- 8.1. Balancing prevention package against undue inducement worries
 - 8.2. Community understanding of scientific concepts
 - 8.3. Finding funding
 - 8.4. Tension between science and ethics
 - 8.5. Threats to trial feasibility/scientific validity
 - 8.6. Variation across sites/protocols
 - 8.7. Working around sponsor policy

B. SERVICE DELIVERY PRACTICES AND PERSPECTIVES (Reducing risk of HIV infection)

1. The standard package of HIV prevention
- 1.1. Access strategies
 - 1.1.1. On-site provision
 - 1.1.1.1. Benefits
 - 1.1.1.1.1. Efficient delivery of services
 - 1.1.1.1.2. Improved control
 - 1.1.1.1.3. Improved monitoring
 - 1.1.1.1.4. Improved retention
 - 1.1.1.1.5. One-stop shop for participants
 - 1.1.1.2. Challenges
 - 1.1.1.2.1. Participant dependency
 - 1.1.1.2.2. Researcher's dilemma
 - 1.1.2. Referral
 - 1.1.2.1. Assisted referrals
 - 1.1.2.2. Benefits
 - 1.1.2.3. Challenges
 - 1.1.2.3.1. Long waiting periods to access services
 - 1.1.2.3.2. Provider attitudes
 - 1.1.2.3.3. Provider knowledge
 - 1.1.2.3.4. Quality of care in the public healthcare sector
 - 1.1.2.3.5. Variable access to prevention services
 - 1.1.2.3.6. Concerns about confidentiality
 - 1.1.2.4. Establishing relationships with providers

- 1.1.2.5. Follow up
 - 1.1.2.6. Private healthcare services
 - 1.1.2.7. Public healthcare services
- 1.2. Documenting the standard of prevention
 - 1.2.1. Keeping records
 - 1.2.2. SOPs and other site documents
 - 1.2.3. The informed consent form
 - 1.2.4. The protocol
- 1.3. For non-trial participants
- 1.4. General education on HIV prevention
- 1.5. Monitoring the standard of prevention
 - 1.5.1. Adverse event reporting
 - 1.5.2. For quality
 - 1.5.3. For uptake
 - 1.5.4. What is monitored
 - 1.5.5. Who monitors
- 1.6. Education on HIV prevention
- 1.7. Counselling
 - 1.7.1. HIV Counselling and Testing
 - 1.7.2. Risk-reduction counselling
 - 1.7.2.1. Rationale
 - 1.7.2.2. Implementation
 - 1.7.2.2.1. Risk-assessment
 - 1.7.2.2.2. Risk-reduction plans
 - 1.7.2.2.3. Checklist/worksheet
 - 1.7.2.2.4. Guidelines
 - 1.7.2.3. Couples counselling
 - 1.7.2.4. Counsellor training
 - 1.7.2.5. Challenges
 - 1.7.2.5.1. Participant behaviour change
 - 1.7.2.5.2. Participant social desirability
 - 1.7.2.6. Areas for improvement
- 1.8. Condoms
 - 1.8.1. Rationale
 - 1.8.2. Implementation
 - 1.8.2.1. Condom negotiation skills
 - 1.8.2.2. Condom demonstrations
 - 1.8.3. Non-trial participants
 - 1.8.3.1. Volunteers at screening
 - 1.8.3.2. Partners
 - 1.8.3.3. Community
 - 1.8.4. Complexities
 - 1.8.4.1. Condom acceptability/uptake
 - 1.8.4.2. Access to condoms
 - 1.8.4.3. Staff chart-noting of condom provision (Participants pressured to use condoms)
 - 1.8.5. Procurement of condoms
 - 1.8.5.1. Providing feedback to DoH

1.9. STI Treatment

- 1.9.1. Rationale
- 1.9.2. Source of funding
- 1.9.3. Implementation
 - 1.9.3.1. Syndromic management
 - 1.9.3.2. Diagnostic tests
 - 1.9.3.3. Guidelines
 - 1.9.3.4. On-site provision
 - 1.9.3.5. Referral
 - 1.9.3.6. Following up participants
 - 1.9.3.7. Counselling on STIs
- 1.9.4. Source of funding
- 1.9.5. Procuring medication
- 1.9.6. Non-trial participants
 - 1.9.6.1. Volunteers at screening
 - 1.9.6.2. Partners
 - 1.9.6.3. Community
- 1.9.7. Complexities
 - 1.9.7.1. Funding of STI treatment
 - 1.9.7.2. Syndromic management
 - 1.9.7.3. Complexities with referral
 - 1.9.7.4. Adherence to treatment
 - 1.9.7.5. No evidence for efficacy

1.10. Post-exposure prophylaxis (PEP)

- 1.10.1. Rationale
- 1.10.2. Implementation
 - 1.10.2.1. Guidelines/SOPs
 - 1.10.2.2. Counselling on PEP
 - 1.10.2.3. Uptake of PEP
- 1.10.3. Source of funding
- 1.10.4. Procuring medication
- 1.10.5. Non-trial participants
 - 1.10.5.1. Volunteers at screening
 - 1.10.5.2. Partners
 - 1.10.5.3. Community
- 1.10.6. Complexities
 - 1.10.6.1. Restrictions on PEP administration
 - 1.10.6.2. Accessibility of PEP
 - 1.10.6.3. Impact on trial feasibility
 - 1.10.6.4. Implementation complexities
 - 1.10.6.5. Participant misuse of PEP
 - 1.10.6.6. Provider attitudes to PEP
 - 1.10.6.7. No evidence for efficacy

1.11. Male circumcision

- 1.11.1. Rationale
- 1.11.2. Implementation
 - 1.11.2.1. On-site
 - 1.11.2.2. Referral
 - 1.11.2.2.1. Establishing relationship

- 1.11.2.2. Follow-up
 - 1.11.2.3. Counselling on VMMC
 - 1.11.2.4. Uptake of VMMC
 - 1.11.3. Source of funding
 - 1.11.4. Non-trial participants
 - 1.11.4.1. Volunteers at screening
 - 1.11.4.2. Partners
 - 1.11.4.3. Community
 - 1.11.5. Complexities
 - 1.11.5.1. Availability of VMMC in the public healthcare sector
 - 1.11.5.2. CAB concerns about VMMC
 - 1.11.5.3. Traditional versus medical circumcision
 - 1.11.5.4. Cultural taboos around discussing VMMC
 - 1.11.5.5. Variable uptake across sites
 - 1.11.5.6. VMMC as an inducement to participate
- 2. Access strategies
 - 2.1. On-site provision
 - 2.1.1. Benefits
 - 2.1.1.1. Improved control
 - 2.1.1.2. Improved monitoring
 - 2.1.1.3. One-stop shop for participants
 - 2.1.2. Challenges
 - 2.1.2.1. Researcher's dilemma
 - 2.1.2.2. Participants dependent on site for services
 - 2.2. Referral
 - 2.2.1. Public healthcare services
 - 2.2.2. Private healthcare services
 - 2.2.3. Benefits
 - 2.2.4. Challenges with referral
 - 2.2.4.1. Quality of care in the public healthcare system
 - 2.2.4.2. Variable access to prevention services across sites
 - 2.2.5. Establishing relationships with services providers
 - 2.2.6. Follow-up
 - 2.2.7. Capacity building
 - 2.3. Post-trial access
- 3. Justifying the standard of prevention
 - 3.1. An ethical obligation
 - 3.2. Non-maleficence (reducing risk)
 - 3.3. Reciprocal justice
 - 3.4. To facilitate informed decision-making
 - 3.5. The right thing to do
- 4. Monitoring the standard of prevention
 - 4.1. For uptake
 - 4.2. For quality
 - 4.3. What is monitored?
 - 4.4. Who monitors?
- 5. Documentation practices

- 5.1. The protocol
- 5.2. Informed consent forms/process
- 5.3. Keeping records
- 6. PERSPECTIVES ON STATE OF THE ART STANDARD OF PREVENTION
 - 6.1. Unpacking state of the art
 - 6.2. Support for a state of the art prevention package
 - 6.3. Objections to a state of the art prevention package
 - 6.3.1. Undue inducement
 - 6.3.2. Behavioural disinhibition
 - 6.3.3. Inequities between participants and community
- 7. Challenges regarding implementing state of the art standard of prevention
 - 7.1. Difficult to explain partial efficacy
 - 7.2. Participants substitute old with the new interventions
 - 7.3. Behaviour change is complex
 - 7.4. CAB access to participants
 - 7.5. De-motivated counsellors
 - 7.6. Funding
 - 7.7. Donor restrictions
 - 7.8. Government policies

C. PERSPECTIVES ON ETHICAL GUIDELINES

- 1. Perspectives on stakeholder consultation
 - a. (Qualified) support for stakeholder consultations
 - b. Objections to stakeholder consultations
 - c. Recommendations for stakeholder consultation
 - d. Rationale for stakeholder consultation
- 2. Perspectives on state of the art standard
 - a. Local state of the art
 - b. Support for state of the art prevention
 - c. Objections to state of the art prevention
 - d. Unpacking state of the art
- 3. Accessibility of guidelines
- 4. Adherence to ethical guidelines
- 5. Awareness (unawareness) of ethical guidelines
- 6. Context-specific application (interpretation) of guidelines
- 7. Tension between state of the art and stakeholder consultation requirements
- 8. Value of ethical guidelines for standards of prevention

Appendix 9: Recommendations related to norms, perspectives and practices

Recommendations related to norms (ethics guidelines)

South African ethics guidelines (MRC, 2003) should be updated to reflect recent evolutions in HIV prevention.

Future revisions of MRC (2003) guidelines should consider providing some direction on strategic partnerships in ensuring access to prevention interventions.

International guidelines (UNAIDS/AVAC, 2011; UNAIDS/WHO, 2012) should consider clarifying vague concepts and/or developing frameworks to facilitate the operationalisation of vague concepts.

Empirical data from this study have illuminated the internal conflict in guidelines between substantive norms requiring access to state-of-the-art prevention interventions, and procedural norms recommending consultation and negotiation of the prevention package. Guidelines should offer clearer direction about how to resolve conflicts between substantive recommendations and stakeholder inputs.

Careful consideration should be given to recommended decision-making process of negotiation and agreement given findings of the pervasiveness of power inequities between HVT stakeholders. Guidelines should therefore carefully consider alternative mechanisms for standard of prevention decision-making, which are constructive and engender collaboration rather than opposition.

Guidance should clarify standard of prevention obligations to non-trial participants.

Guidance should clarify whether the standard of prevention differs based on participants' vulnerability/phase of the trial.

Guidance should provide direction on some of the complexities with standards of prevention faced by trial implementers such as the potential for different standards of prevention within countries (between different trials and sites), provider-promotion, participant uptake and the influence of socio-cultural norms on standard of prevention decision-making.

Recommendations related perspectives and practices (by stakeholder group)
Sponsors should clarify their funding policy in a way that clearly indicates which prevention services are permitted, and which is cognisant of ethical requirements to ensure access to standard of prevention interventions.
HVT trial implementers and community representative structures should explore alternative mechanisms to ensure stakeholder inputs on standards of prevention.
HVT implementers should establish creative partnerships and diversify funding sources.
As trial site capacity expands, new sites should engage the DoH as a potential procurement source and referral centre.
Sites should endeavour to evaluate and monitor the quality of prevention interventions, including provider-promotion of services.
Sites should consider strategies to improve access to female condoms, including lobbying HIV prevention activist groups in advocating for improved accessibility of female condoms.
Given the potential for dispensing practices to impact on condom uptake, sites should consider ensuring access to female condoms outside counselling sessions.
Protocols and consent forms should contain more information on the standard of prevention. Alternatively an additional fact sheet on the standard of prevention could be provided to participants.
The capacity of CABs to review protocols in terms of standards of prevention, and the scientific implications for study design, should be actively built.
Consideration should be given to including a CAB representative at each site on local RECs that review HIV prevention trial protocols.
RECs should consider revising ethics application forms to require detailed information on the standard of prevention that will be provided to participants, and efforts (if any), to monitor the provision of these service.
RECs should request that sites document efforts (and challenges) in implementing GPP guideline requirements.
RECs could benefit from intensive ethics training including on mechanisms to enhance their interrogation of substantive issues, such as the standard of prevention.

Recommendations for future research

Given findings that socio-cultural norms may constrain CAB inputs on the standard of prevention, and impact on provider-promotion and participant uptake of prevention interventions, more detailed research should be undertaken that clarifies the extent to which gender norms and cultural prescriptions influence the realisation of recommendations in ethics guidelines.

Future research should pilot and evaluate existing frameworks that propose procedural decision-making processes (e.g., Tarantola et al., 2007) that take into account some of the challenges with consultation reported in this study.

The perspectives of stakeholders should be canvassed regarding the value of frameworks (e.g., Jay et al., n.d.) that attempt to offer operational guidance on when to add new methods to the prevention package.

There is a critical gap in knowledge with regard to the threshold at which adding new prevention methods will invalidate trials.
